EXTRANEAL™ (7.5% Icodextrin)
Peritoneal Dialysis Solution

NDA 21-321

CARDIO-RENAL ADVISORY COMMITTEE
BRIEFING DOCUMENT

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BAXTER HEALTHCARE CORPORATION

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I. EXECUTIVE SUMMARY

Advanced renal failure is a critical condition that requires the institution of life-saving therapies such as transplantation, hemodialysis and peritoneal dialysis. The immediate and long-term goals of these therapies are to remove accumulated toxins and maintain fluid and electrolyte balance. In the absence of timely institution of these renal replacement therapies, the patient faces a rapid downhill course of debilitation and eventual death.

Peritoneal dialysis (PD) is an established therapy that meets the immediate and long-term goals of removing toxins and maintaining fluid balance in patients with terminal renal failure. Under current conditions of clinical practice in the United States, peritoneal dialysis is performed with the use of dialysis solutions that utilize dextrose (glucose monohydrate) as an osmotic agent. The role of dextrose in these solutions is to act as the driving force for the removal of fluid, also referred to as ultrafiltration (UF). The effectiveness of dextrose in this role is concentration dependent. Peritoneal dialysis solutions typically contain dextrose at concentrations of 1.5%, 2.5% and 4.25%. Physicians will escalate the concentration used in their patients depending on the clinical needs. Typically, a patient will use four exchanges per 24 hours in continuous ambulatory peritoneal dialysis (CAPD) The proportions of the various dextrose concentrations used for these exchanges vary based on clinical needs. The 1.5% and 2.5% are the most commonly used concentrations with the 4.25% being relegated to cases of gross fluid overload or clinical failure to achieve adequate fluid removal with the lower concentrations.

The role of dextrose as the driving force for ultrafiltration in PD is hampered by opposing factors in the peritoneal cavity, namely tissue and lymphatic absorption of fluid, and by the transience of dextrose levels within the peritoneal cavity because of rapid absorption of the sugar. As a small molecule, over 75% of the initial mass of dextrose is absorbed within 4 hours of instillation. This results in dissipation of the osmotic gradient leading to cessation of active fluid removal, and leaves absorptive processes unopposed. For therapy cycles that are short such as during nighttime automated PD (APD) or during daytime in CAPD, these drawbacks of dextrose are not very limiting. Neither form of therapy, however, can rely on a limited period of short dwells. Toxin removal for small solutes in many patients requires extension of the therapy for a full 24-hour period. More important, however, is the obligatory need of sustained full diurnal therapy for the removal of middle molecular weight toxins which is time-dependent and requires the presence of fluid in the abdomen for a full diurnal cycle.

These requirements to meet the toxin removal needs of the patient, coupled with the practical logistics of a self-administered home based therapy have resulted in the utilization of a long dwell (8 hours or more) in peritoneal dialysis. It is in this long-dwell component of PD therapy that the limitations of dextrose as the motive force for ultrafiltration are readily apparent. In CAPD, nearly 1 out of every 4 patients retains fluid during the long dwell, which is typically 8 to 10 hours. In APD where the typical long dwell can extend up to 15 hours, nearly 3 out of every 4 patients retain fluid (referred to as negative net ultrafiltration). When faced with negative net ultrafiltration in the long dwell, a clinician will attempt to compensate by increasing fluid removal during the shorter cycles using higher dextrose concentrations. Alternatively, clinicians will rely on 4.25% dextrose for the long dwell. While glucose concentrations continue to fall precipitously, the higher starting value leads to an osmotic gradient that is maintained for a longer period. However, at this concentration, a large and dramatic amount of ultrafiltration occurs early in the dwell, which is frequently experienced by the patient as a sense of distension and fullness that can be uncomfortable. In addition, use of higher dextrose concentrations result in greater glucose absorption and greater glucose exposure of the peritoneal membrane, a process thought to have detrimental effects (hyperlipidemia, weight gain, and possible alterations in the peritoneal membrane).

Icodextrin, a polymer of glucose, was developed to address the shortcoming of dextrose as an osmotic agent for the long dwell in peritoneal dialysis. Specifically, the aims of Extraneal clinical trials were to demonstrate that it is effective as a dialysis solution in peritoneal dialysis, that its effect is sustained over the course of the long dwell (minimizing negative ultrafiltration), and that its safety profile is comparable to the currently available dextrose solutions.

The structure of icodextrin is similar to glycogen, consisting of oligosaccharide polymers of D-glucopyranose linked by alpha (1-4) and alpha (1-6) glucosidic bonds. It differs from glycogen in that it has a lower percentage of alpha (1-6) linkages, and hence, is less highly branched. Because of its high molecular weight (12-20,000 kda), icodextrin is more slowly absorbed across the peritoneal membrane compared to dextrose. This permits sustained ultrafiltration during dwells longer than 8 hours, resulting in greater fluid removal as compared to dextrose. Examination of the pharmacokinetics of the compound confirms the theoretical predictions based on its molecular weight: it is slowly removed from the peritoneal cavity predominantly by slow lymphatic absorption. After a mean dwell of 12 hours, only 40% of the polymer is absorbed from the peritoneal cavity, whereas over 75% of dextrose is absorbed in only 4 hours. The differential rate of removal from the peritoneal cavity is responsible for the predicted and observed increased efficiency of icodextrin over dextrose during the long dwell.

In clinical trials including 216 Extraneal patients and 207 dextrose control patients, the data demonstrate unequivocally the effectiveness of Extraneal for use in long dwell peritoneal dialysis. Compared to 1.5% and 2.5% dextrose solutions, Extraneal consistently provided statistically higher net UF, solute clearance, and lower negative net UF over the long dwell period of 8-16 hours. In one study, Extraneal resulted in ultrafiltration similar to 4.25% dextrose for 8-hour dwells, and a trend towards greater ultrafiltration at 12 hour dwells. The hallmark of Extraneal's success is its correction of a clinical problem observed under common conditions of clinical practice: the negative ultrafiltration observed with 1.5% and 2.5% in the long dwell. This success has been documented uniformly in all the controlled studies described in this document.

From a safety perspective, data from these 493 Extraneal patients and 347 control patients demonstrate that Extraneal is safe and well tolerated as a peritoneal dialysis solution. Patients included in this summary had a mean exposure to Extraneal of almost 6 months (232.5 days) and a maximum exposure of more than 44 months (1326 days).

The overall adverse event profile for Extraneal -treated patients was generally similar to that of active control patients in incidence rates and assessments of severity. Slightly more Extraneal patients had one or more adverse events considered possibly, probably, or definitely related to study drug (28.2% Extraneal, 25.7% control). Observational data on mortality did not show any statistically significant differences in survival time between groups and no deaths in either treatment group were considered related to study drug.

Extraneal-treated patients had a 5.5% higher incidence of rash compared to the control population (10.1% vs. 4.6%). This difference was statistically significant. However, most events were mild to moderate in severity and disappeared with continued treatment or discontinuation. Analysis of commonly reported adverse events occurring after 6 months and 12 months of Extraneal therapy were generally lower than the overall incidence of these adverse events; there appears to be no cumulative adverse effect of Extraneal.

Extraneal-treated patients had lower sodium and chloride levels compared to dextrose-treated patients but these values remained within the normal limits over the course of treatment. Extraneal-treated patients experienced higher alkaline phosphatase levels compared to control and did not result in any abnormal clinical sequelae. Serum amylase levels in Extraneal patients were markedly lower than control patients due to interference from icodextrin with amylase activity in the assay.

In conclusion, Extraneal is uniquely suited for the long dwell exchange in PD. Extraneal demonstrated a desirable clinical effect of increased ultrafiltration and decreased the percentage of patients with negative net ultrafiltration compared with the commonly used concentrations of dextrose (1.5% and 2.5%). Data from one study suggest Extraneal may be as effective as 4.25% dextrose during longer dwells of 12 hours or more. Except for a self-limited and readily reversible skin side effect, its safety profile is comparable to currently used dextrose based solutions. It is therefore uniquely suited to fulfil the need for sustained ultrafiltration during the long dwell in peritoneal dialysis.

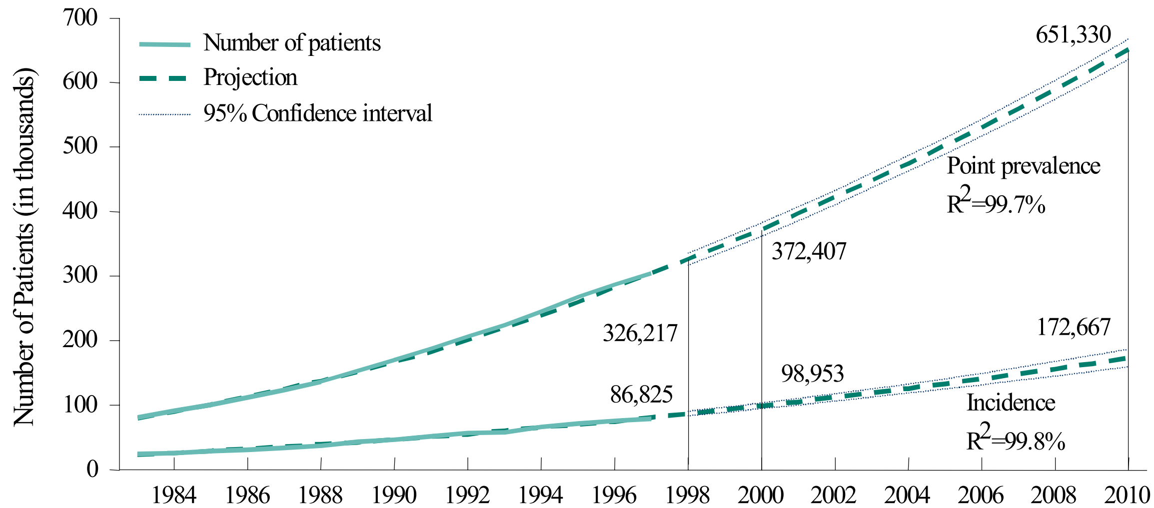
1.0 INTRODUCTION

1.1 Background on End Stage Renal Disease

End stage renal disease (ESRD) is defined as the state at which irreversible loss of endogenous renal function results in major erosion of a patient's health and jeopardizes the survival of the patient unless renal replacement therapy is initiated. ESRD is a critical condition that requires the institution of life-saving therapies such as transplantation, hemodialysis and peritoneal dialysis. The immediate and long-term goals of these therapies are to remove accumulated toxins from protein metabolism and maintain fluid and electrolyte balance. In the absence of timely institution of these renal replacement therapies, the patient faces a rapid downhill course of debilitation and eventual death. Kidney transplantation is generally accepted as the optimal form of renal replacement therapy in that it provides patients the best prognosis for survival and quality of life.[1] However, given the rapid rise in the incidence of ESRD in the United States and other countries and the continued shortage of donor kidneys, most patients with ESRD will require dialysis at some time during their life.

In 1998, 85,520 new ESRD patients entered the dialysis or transplant population for an incidence rate of 308 patients per million U.S. inhabitants and a prevalence rate of 1160 patients per million inhabitants. This incidence rate is the highest in the world, followed by Japan with 234 new patients per million inhabitants. The projected number of U.S. patients with ESRD is expected to reach 651,000 by 2010 (**Figure 1A**).[2]

Figure 1A: Actual and projected incidence and prevalence of new ESRD patients (projected to 2010).



1.2 Clinical Management of ESRD with Peritoneal Dialysis

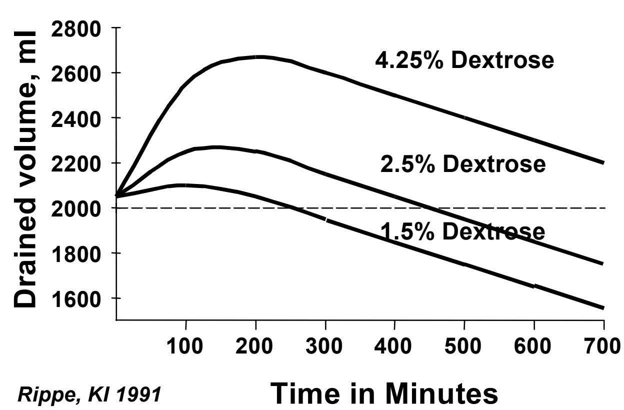
Current peritoneal dialysis therapy is practiced by infusion of hypertonic, sterile, pyrogen-free dialysis solution into the peritoneal cavity. The solution (1.5-3.0 L) is allowed to dwell for a period of time ranging from 0.5 to 16 hours, depending on the prescription and mode of therapy, and then drained from the peritoneal cavity. The period of time the fluid remains in the peritoneal cavity is called the dwell time and the draining and infusion of the dialysis solution is called an exchange. Patients either make several manual exchanges during the day (4 to 6 hours per dwell) and one manual exchange overnight for an 8 to 12-hour dwell (continuous ambulatory peritoneal dialysis (CAPD)) or utilize a cycler to deliver their dialysis therapy (automated peritoneal dialysis (APD)). Patients who use a cycler usually receive several rapid exchanges during the night lasting for 0.5 to 2 hours and one or two longer dwells during the day. These daytime dwells typically last for 8 to 16 hours.

Ultrafiltration (fluid removal) in peritoneal dialysis is governed primarily by the osmotic gradient between the blood and the solution in the peritoneal cavity. This gradient drives water from tissue capillaries lining the peritoneal cavity, through small pores in the capillary membranes, across the peritoneal membrane and into the peritoneal cavity. This osmotic force should be able to produce approximately 1 to 2 liters of ultrafiltration per day in order to maintain proper fluid balance in an adult peritoneal dialysis patient. Currently available peritoneal dialysis solutions use dextrose (glucose monohydrate) as the osmotic agent. The effectiveness of dextrose in this role is concentration dependent.

Peritoneal dialysis solutions typically contain dextrose in concentrations of 1.5%, 2.5% and 4.25%. In the United States, 56% of the usage is 2.5% dextrose, 32% is 1.5% and 12% is 4.25% dextrose (Baxter 2000 Marketing data). Physicians will escalate the concentration used in their patients depending on the clinical needs. Typically, a patient will use four exchanges per 24 hours in CAPD. The proportions of the various dextrose concentrations for these exchanges vary based on clinical needs. The 1.5% and 2.5% are the most commonly used formulations with the 4.25% being relegated to cases of gross fluid overload or clinical failure to achieve adequate fluid removal with the lower concentrations.

Because of the rapid absorption of glucose from the peritoneal cavity, the osmotic gradient declines rapidly, leading to a decline in the rate of ultrafiltration with increasing dwell times. As a result, the ultrafiltration profile changes dramatically throughout the dwell (**Figure 1B**).[3] For example, during a 4-5-hour dialysis dwell with 2.0 L of a standard 1.5% dextrose solution, ultrafiltration is greatest at the beginning of the dwell when the osmotic gradient is maximal, creating a net ultrafiltration of ~150-200 ml after 2 hours. As the dwell progresses, however, the rate of ultrafiltration declines, and after 3-4 hours there is usually net fluid reabsorption. For a solution containing 4.25% dextrose, the osmotic gradient is greater, resulting in a net ultrafiltration of ~400-600 ml at two hours; nevertheless, after 3 hours, peritoneal volume begins to decline. The ultrafiltration profile of dextrose-based solutions is therefore best suited for short dialysis dwells.

Figure 1B: Ultrafiltration profile of Dextrose



The role of dextrose as the driving force for ultrafiltration in PD is hampered by opposing factors in the peritoneal cavity, namely tissue and lymphatic absorption of fluid, and by the transience of dextrose levels within the peritoneal cavity because of its rapid absorption. This results in dissipation of the osmotic gradient leading to cessation of active fluid removal, and leaves absorptive processes unopposed. For therapy cycles that are short such as during night time automated PD (APD) or during daytime in CAPD, these drawbacks of dextrose are not very limiting. Neither form of therapy, however, can rely on a limited period of short dwells. Toxin removal for small solutes in many patients requires extension of the therapy for a full 24-hour period. More important however is the obligatory need of sustained full diurnal therapy for the removal of middle molecular weight toxins which is time-dependent and requires the presence of fluid in the abdomen for a full diurnal cycle.

These requirements to meet the toxin removal needs of the patient, coupled with the practical logistics of a self-administered home based therapy have resulted in the utilization of a long dwell (8 hours or more) in peritoneal dialysis. It is in this long-dwell component of PD therapy that the limitations of dextrose as the motive force for ultrafiltration are most apparent. In CAPD, nearly 1 out of every 4 patients retains fluid during the long dwell, which is typically 8 to 10 hours. In APD where the typical long dwell can extend up to 15 hours, nearly 3 out of every 4 patients retain fluid.

When faced with negative ultrafiltration in the long dwell, a clinician will usually attempt to compensate by increasing fluid removal during the shorter cycles using higher dextrose concentrations. Alternatively, clinicians will rely on 4.25% dextrose for the long dwell. At this concentration, a large and dramatic amount of ultrafiltration occurs early in the dwell, which is frequently experienced by the patient as a sense of distension and fullness that can be uncomfortable. In addition, higher concentrations of dextrose are thought to result in hyperlipidemia, weight gain and potential adverse effects on the peritoneal membrane.

To address these concerns, Baxter Healthcare has developed a PD solution with a unique osmotic agent, icodextrin, with the trade name Extraneal™. Extraneal is intended for use in the long dwell exchange of PD therapy to allow greater net ultrafiltration and solute clearances compared to current dextrose-based PD solutions.

1.3 Description of Extraneal Peritoneal Dialysis Solution

Extraneal is a peritoneal dialysis solution containing 7.5% (w/v) icodextrin as the primary osmotic agent. The formulation of Extraneal is shown in Table 1A.

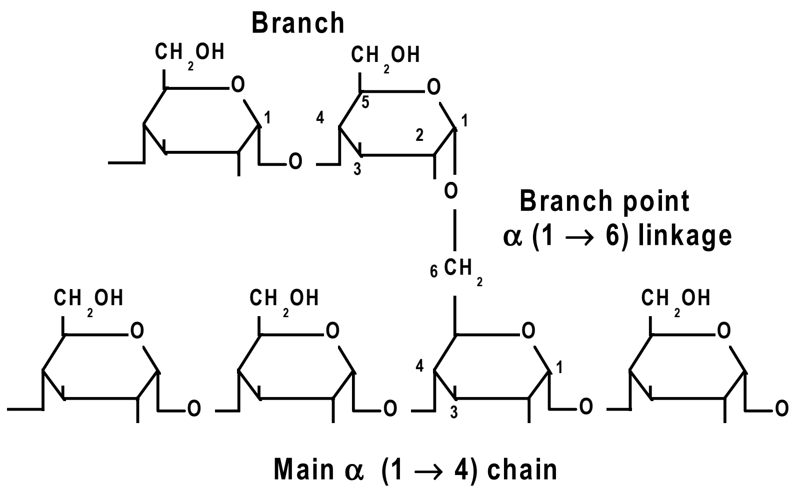
Table 1A: Formulation of Extraneal™ 7.5% (w/v) Icodextrin PD Solution

Icodextrin (g/dL)	7.5
Sodium (mEq/L)	132.0
Chloride (mEq/L)	96.0
Calcium (mEq/L)	3.5
Magnesium (mEq/L)	0.5
Lactate (mEq/L)	40.0
pH	5.2
Osmolality (mOsm/L)	282-285

The electrolyte composition and buffer (lactate) are identical to the PD-2 formulation of Dianeal (an approved solution for peritoneal dialysis currently marketed in the US).

Icodextrin is a soluble, polydispersed, high molecular weight polymer of glucose isolated by fractionation of hydrolyzed cornstarch. The structure of icodextrin is similar to glycogen, consisting of oligosaccharide polymers of D-glucopyranose linked by alpha (1-4) and alpha (1-6) glucosidic bonds. The structure of icodextrin differs from glycogen in that icodextrin has a lower percentage of alpha (1-6) linkages (<10%) and is hence less highly branched. A representation of the structure of icodextrin, showing the main alpha (1-4)-linked chain and alpha (1-6) branching, is presented in **Figure 1C**.

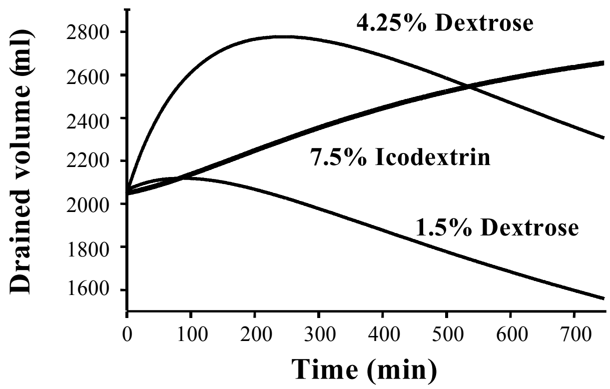
Figure 1C: Representation of the Structure of Icodextrin



Because of its higher molecular weight, icodextrin acts as a colloid osmotic agent rather than a crystalloid osmotic agent.[4] The process of colloid osmosis is based on the principle that fluid flow across a semi-permeable membrane occurs in the direction of the relative excess of impermeable large solutes, rather than along its osmolarity gradient. As a result, PD solutions containing icodextrin are able to effect transcapillary ultrafiltration (UF) while remaining essentially isosmolar with respect to plasma (~285 mOsm/L). By contrast, dextrose-containing solutions are significantly hyperosmolar to plasma, ranging from 346 to 485 mOsm/L.

Due to its high molecular weight, icodextrin is more slowly absorbed across the peritoneal membrane compared to dextrose. Crystalloid osmotic agents such as glucose are absorbed across the peritoneal membrane by diffusion and convection, the latter process resulting from fluid movement out of the peritoneal cavity primarily via lymphatic pathways. For colloid osmotic agents such as icodextrin, the diffusive component is minimized, and only convection contributes substantially to their loss from the peritoneal cavity. As a result, the osmotic pressure created by icodextrin is relatively constant, leading to a slow, continuous increase in peritoneal volume and greater net ultrafiltration at the end of a long dwell (**Figure 1D**).[5] Consequently, Extraneal was developed for application for long dialysis dwells.

Figure 1D: Peritoneal Volume Profiles for Icodextrin and Dextrose-Containing PD Solutions



2.0 REGULATORY HISTORY OF EXTRANEAL

2.1 Current Marketing Status of Extraneal Worldwide

As of January 2001, Extraneal is approved in 28 countries and has been used by at least 21,000 patients worldwide since it's initial launch in Europe 7 years ago (**Table 2A**). There are currently 6,836 patients on product in Europe representing approximately 29% of the total European PD patient population.

Table 2A: Foreign Marketing Approval for Extraneal (June 2001)

Marketing Approval Granted					
Austria	Czech Repub.	Greece	Korea	Poland	Sweden
Belgium	Denmark	Hong Kong	Luxemburg	Portugal	Switzerland
Brazil	Finland	Ireland	Malta	Singapore	United Kingdom
Canada	France	Israel	Netherlands	Slovakia	
Columbia	Germany	Italy	Norway	Spain	
Marketing Applications Filed					
Argentina	Australia	Japan	New Zealand	Romania	Slovenia
Turkey	Lithuania				

Since initial commercialization, there are a total of almost 200,000 patient months exposure with Extraneal with approximately 10% of this exposure in clinical trials (**Table 2B**).

Table 2B: Patient Exposure* (February 1st 1997-January 31st 2001)

ACTIVITY	PATIENT MONTHS
Clinical Trials (Company sponsored)	1,921.1
Compassionate Use (World-wide)	2,429.6
Market Experience (World-wide)	187,081.3
TOTAL EXPOSURE	**191,432**

* Calculations based on patient using 1 bag per day, 30 bags per month, to arrive at patient months

2.2 US Regulatory History

The original IND for Extraneal was submitted to FDA's Division of Metabolic and Endocrine Drug Products in November 1996. The IND was filed with a Phase III open-label active controlled clinical trial to evaluate the safety and efficacy of Extraneal as a replacement peritoneal dialysis solution for Dianeal for the daytime dwell exchange (i.e. 12-16 hour duration) in patients with ESRD on APD. It was Baxter's intent to submit an NDA based upon the foreign clinical studies, used to grant European Approval, and the proposed controlled Phase III clinical trial. Shortly after this submission, the IND was transferred to the Division of Cardio-Renal Drug Products (DCRDP).

DCRDP considered the IND open indicating that study could proceed with Extraneal in patients. However, input from DCRDP resulted in the following modifications to the clinical development plan:

1. Two double blind studies would be conducted comparing Extraneal to 2.5% dextrose Dianeal for the long dwell exchange: a one month efficacy and safety study (RD-97-CA-130); and a 12-month long term safety study planned to include approximately 150 patients exposed to Extraneal (RD-97-CA-131).

2. In the 12-month safety study, Baxter would evaluate mortality and body weight in addition to standard safety measures.

On October 19, 2000, a closed session of the Cardio-Renal Advisory Committee was held with Baxter to discuss clinical development of PD solutions (**parenthetical numbers refer to block in meeting transcript**). Because PD patients constitute a very limited population with high morbidity and mortality, unique issues for the development of peritoneal dialysis solutions exist. At this meeting, it was agreed that fluid removal (ultrafiltration) was an acceptable endpoint for clinical efficacy (242). In order to evaluate product safety, the Advisory Members identified the following three categories of PD solution development, delineated based upon how a product would differ from existing solutions:

1. Category 1: same dialysate, minor changes to constituents with no expected impact on safety and efficacy (183/184) with 50 patients in the treatment arm and 50 in the control group treated over 3 months (192).

2. Category 2: material change to the dialysate, no claim of additional benefits, need to show that solution was an effective dialysate as well as demonstrate that the change in dialysate did not alter key safety issues from current therapy (184). A patient range of 400-800 (237) and duration of 3 months minimum with 6-12 months preferred (252).

3. Category 3: meaningful benefit over current therapy with the risk-to-benefit- in the patient's favor (184). A patient range of 400-800 patients (237) and duration as in category 2.

The committee also discussed examples of meaningful benefits, including fluid balance, reduction of edema, and improved ultrafiltration (241-247).

Extraneal has been granted Orphan Drug Designation by the FDA in July 1997. On December 20, 2000, the NDA for Extraneal was submitted to the Division of Cardio-Renal Drug Products.

3.0 CLINICAL DEVELOPMENT PROGRAM

3.1 Clinical Development and Studies Summary

The clinical database used to evaluate the safety and efficacy of Extraneal consists of 9 studies involving a total of 840 patients, 493 of which were exposed to Extraneal (see **Appendix 1** for Study Synopses). A total of 197 patients are counted more than once due to study design (cross-over, rollover extension or sub study). The safety patient population consists of 643 unique patients and the efficacy patient population consists of 423 unique patients.

Studies were designated as “Key” or “Supportive”. Key studies were those considered to meet all of the requirements of adequate and well-controlled studies, per 21 CFR 314.126, intended to demonstrate efficacy and or safety for the proposed indication. Key studies for safety and efficacy are RD-97-CA-130, MIDAS (ML/IB001), PRO-RENAL-REG-035, and for safety RD-97-CA-131. Supportive studies were additional studies, which provide evidence for evaluation of the safety and or efficacy of Extraneal, but were intended to evaluate specific effects (e.g. pharmacokinetics, uncontrolled extension, etc.). Supportive studies included RD-99-CA-060, MIDAS-2 (ML/IB004), DIANA (ML/I011), MIDAS S-5 (ML/IB014), and DELIA (ML/IB009). The integrated database for safety included data from both the Key and Supportive studies. A summary of patients in the key and supporting studies is presented in **Table 3A**.

The terms “control” or “active control” refer to the comparator dextrose-containing peritoneal dialysis solution and are used interchangeably throughout this document.

A tabular summary of all studies can be found in the Table of All Studies (**Table 3B**).

Table 3A: Summary of Patients

Number of Patients Evaluated for Safety						
Study	**Total Number of Patients evaluated for safety**			**Number of Unique Patients***		
	Control	**Icodextrin**	**Total**	**Control**	**Icodextrin**	**Total**
RD-97-CA-130	85	90	175	85	90	175
ML/IB/001 (MIDAS)	103	106	209	103	106	209
PRO-RENAL-REG-035	19	20	39	19	20	39
RD-97-CA-131	112	175	287	50	108	158
ML/IB/020 (DELIA)	9	10	19	1	10	11
ML/IB/011 (DIANA)	19	19	38	19	19	38
ML/IB/004 (MIDAS-2)	0	48	48	0	0	0
ML/IB/014 (S5)	0	12	12	0	0	0
RD-99-CA-060	0	13	13	0	13	13
Total	**347**	**493**	**840**	**277**	**366**	**643**

Number of Patients Evaluated for Efficacy			
Study	**Control**	**Icodextrin**	**Total**
RD-97-CA-130	**85**	**90**	**175**
Efficacy Evaluable	85	90	175
ML/IB/001 (MIDAS)	**103**	**106**	**209**
Efficacy Evaluable	93	85	178
1.5% Dextrose (8-hour dwell)	55	50	105
1.5% Dextrose (12-hour dwell)	55	50	105
2.5%/4.25% Dextrose ((8-hour dwell)	38	35	73
2.5%/4.25% Dextrose (12-hour dwell)	38	35	73
PRO-RENAL-REG-035	**19**	**20**	**39**
Efficacy Evaluable	19	20	39
Total	**207**	**216**	**423**

*The complete database for the safety includes results for 840 patients (347 Control, 493 icodextrin). However, 197 of these patients are included in the safety analyses more than once due to study design (crossover study, rollover extension, or sub-study). Study RD-97-CA-131, a long-term safety study, included 129 patients (62 control, 67 icodextrin) who previously participated in Study RD-97-CA-130. Study ML/IB/020, a crossover study had 11 unique patients, 1 patient received only control, 2 received only icodextrin, and 8 received both treatments. The 48 patients in Study ML/IB/004 (MIDAS-2) were all previously enrolled in ML/IB/001 (MIDAS) and the 12 patients in Study ML/IB/014 (S-5) were previously enrolled in MIDAS-2.

Table 3B: Summary of Extraneal Clinical Studies

Protocol Number	Study Title	Study Description	N	Duration	Mean Age (Range)	% M/F B/W/O
Key Studies						
RD-97-CA-130	A Study to Evaluate the Safety and Efficacy of a 7.5% Icodextrin Peritoneal Dialysis Solution in Patients Treated with CAPD.	Prospective, randomized, double-blind, and parallel group, active-controlled study comparing the efficacy and safety of Extraneal (7.5% icodextrin) with that of Dianeal for the overnight dwell in CAPD patients.	Total =175 I = 90 C = 85	4 weeks	I : 54 (22 - 82) C: 55 (26 - 86)	I: 38/ 62 33/ 53/ 13 C: 31/ 69 32/ 55/ 13
RD-97-CA-131	A Study to Evaluate the Safety of a 7.5% Icodextrin Peritoneal Dialysis Solution in Patients Treated with Peritoneal Dialysis (PD) in North America.	Prospective, randomized, double blind, and parallel group, active-controlled study comparing the safety of Extraneal (7.5% icodextrin) with that if Dianeal for the long dwell in PD patients. Patients treated by both CAPD and APD were included.	Total = 287 I = 175 C = 112	52 weeks	I: 53 (22 - 83) C: 55 (25 - 86)	I: 53/ 47 26/ 63/ 11 C: 45/ 55 28/ 62/ 10
ML/IB/001	Multicenter Clinical Trial of Dextrin 20 in Continuous Ambulatory Dialysis (MIDAS)	Open, randomized, active-controlled, parallel group study comparing the efficacy and safety of 7.5% icodextrin with that of dextrose for the long overnight dwell in CAPD patients.	Total = 209 I = 106 C = 103	6 months	I: 55 (18 - 77) C: 22 - 82 (55)	I: 67/ 33 5/ 89/ 6 C: 65/ 35 3/ 93/ 4
Pro-Renal-Reg-035	A Study to Evaluate the Safety and Efficacy of a 7.5% Icodextrin Solution Peritoneal Dialysis in Patients Treated With Automated Peritoneal Dialysis (APD).	Open-label, randomized, parallel group, active-controlled study to compare the efficacy and safety of Extraneal (7.5% icodextrin) with that of 2.27% glucose (Dianeal PD4) for the long daytime dwell in APD patients.	Total = 39 I = 20 C = 19	16 weeks	I: 46 (27 - 74) C: 45 (26 - 75)	I: 85/ 15 0/ 95/ 5 C: 68/ 32 0/ 100/ 0

Refer to Appendix 1 for study synopses
I = 7.5% icodextrin = Extraneal; C = control; M = male; F = female; B = black; W = white; O= other

Protocol Number	**Study Title**	**Study Description**	**N**	**Duration**	**Age Mean (Range)**	**% M/F B/W/O**
Supportive Studies						
ML/IB/020	Assessment of Icodextrin for the Long Daytime Dwell in Automated Peritoneal Dialysis (APD) Patients (DELIA).	Open, two-way crossover study to evaluate the safety, efficacy, and patient acceptability of icodextrin for the long (14- to 16- hour) dwell in APD patients.	Total = 11 I = 11 7 patients completed both arms	6 weeks per treatment (4-week washout between)	I: 52 (19-66)	I: 27/ 73 0/ 100/ 0
ML/IB/011	Assessment of the Biocompatibility of Glucose Polymer Solution in Automated Peritoneal Dialysis (APD) Patients (DIANA).	Open-label, randomized, active-controlled, parallel group study comparing icodextrin with glucose for the long daytime dwell (12-16 hours) in APD patients in the Netherlands.	Total = 38 I = 19 C = 19	24 months	I: 53 (31-70) C: 51 (21-68)	I: 53/ 47 5/ 79/ 16 C: 89/ 11 5/ 84/ 11
ML/IB/004	Multicenter Clinical Trial of Icodextrin in Continuous Ambulatory Peritoneal Dialysis: Extension Study (MIDAS-2).	Open-label, long-term extension study to evaluate the safety of icodextrin in CAPD patients who have already received 6 months of therapy during the MIDAS study.	Total = 48 I = 48	Varied; until treatment failure	I: 57 (20-77)	I: 75/ 25 4/ 94/ 2
RD-99-CA-060	A Study to Evaluate the Pharmacokinetics of a Single Exchange of 7.5% Icodextrin PDS in Patients Treated with PD	Open, prospective, single exchange, pharmacokinetic study	Total = 13 I = 13	Single, 12-hour dwell; patients followed for 28 days	I: 54 (29-77)	I: 38/ 62 46/ 46/ 8
ML/IB/014	Evaluation of Serum Levels of Icodextrin at Steady State, After Stopping Treatment, and on Re-Starting after Three Weeks (S-5)	Open, prospective pharmacokinetic study; sub-study of MIDAS-2; patients received dextrose solution 1 dwell/day for 3 weeks, then icodextrin solution 1 dwell/day for 2 weeks	Total = 12 12 patients received both treatments	5 weeks (3 weeks dextrose then 2 weeks icodextrin)	I: 58 (22-75)	83/ 17 0/ 100/ 0

Refer to Appendix 1 for study synopses
I = 7.5% icodextrin = Extraneal; C = control; M = male; F = female; B = black; W = white; O= other

3.2 Demographics of Patients Studied

The patient demographics for all 9 studies used in the safety database are presented in **Table 3C**.

Table 3C: Baseline Demographics – All Studies

	Control Group N = 347		Extraneal Group N = 493		All Patients N = 840	
	N	%	N	%	N	%
Age (yrs)						
Mean ± SE	54.1± 0.76		53.9 ± 0.63		54.0 ± 0.48	
18 - <75	328	94.5	472	95.7	800	95.2
≥ 75	19	5.5	21	4.3	40	4.8
Gender						
Male	175	50.4	278	56.4	453	53.9
Female	172	49.6	215	43.6	387	46.1
Race						
Caucasian	257	74.1	360	73.0	617	73.5
Hispanic	10	2.9	14	2.8	24	2.9
Asian	12	3.5	22	4.5	34	4.0
Black	62	17.9	90	18.3	152	18.1
Other	6	1.7	7	1.4	13	1.5
Primary Renal Diagnosis						
Diabetic nephropathy	74	21.3	102	20.7	176	21.0
Hypertensive nephropathy	68	19.6	114	23.1	182	21.7
Glomerulonephritis	68	19.6	87	17.6	155	18.5
Polycystic kidney disease	22	6.3	28	5.7	50	6.0
Interstitial nephritis	11	3.2	23	4.7	34	4.0
Obstructive nephropathy	2	0.6	5	1.0	7	0.8
Autoimmune disease	9	2.6	7	1.4	16	1.9
Other	93	26.8	127	25.8	220	26.2
Diabetic						
Yes	94	27.1	132	26.8	226	26.9
No	244	70.3	350	71.0	594	70.7
Not recorded	9	2.6	11	2.2	20	2.4
Hypertensive*						
Yes	147	42.4	243	49.3	390	46.4
No	200	57.6	250	50.7	450	53.6
Hypertensive Nephropathy						
Yes	68	19.6	114	23.1	182	21.7
No	279	80.4	379	76.9	658	78.3

* Systolic pressure >140 mmHg and/or diastolic pressure >90 mmHg at baseline

No difference between age, gender, race, or comorbid conditions were found between the active control and treated groups.

3.3 Extent of Exposure

Two hundred and fifteen (215) patients were exposed to Extraneal for at least six months and 155 patients were exposed to Extraneal for at least one year. The extent of exposure is summarized by number of days in **Table 3D**.

Table 3D: Duration of Exposure for All Studies

Duration Categories (days)	Control Group		Icodextrin Group	
	N	Percent	N	Percent
<30	78	22.5	103	20.9
30 - <90	51	14.7	75	15.2
90 - <180	93	26.8	100	20.3
180 - <360	50	14.4	60	12.2
>=360	75	21.6	155	31.4
TOTALS	347	100.0	493	100.0

3.4 Rationale for Dosing Regimen

Early feasibility and formulation studies with glucose polymers as an osmotic agent for peritoneal dialysis examined wide ranges in molecular weight distribution and glucose polymer concentrations. Results obtained from these studies demonstrated that glucose polymer fractions with a relatively high molecular weight possessed the most favorable ultrafiltration (efficacy) profile in relation to the amount of carbohydrate absorbed. Overall, the percent absorption of total carbohydrate for glucose polymer-based dialysis solutions was much less than that of dextrose-based solutions. Concentrations of glucose polymer from 5% – 10% were shown to be effective at providing ultrafiltration and were shown to be superior to dextrose containing solutions in sustaining ultrafiltration during long dwells. Based on the results of these feasibility studies, a high molecular weight fraction glucose polymer and concentration of 7.5% were selected for clinical development.

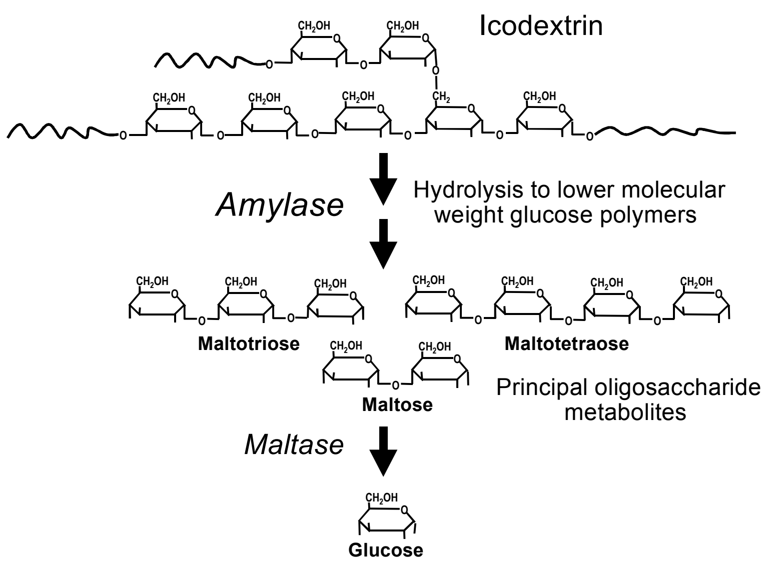
4.0 PHARMACOLOGY AND PHARMACOKINETICS

Extraneal is administered directly into the peritoneal cavity, its site of action, and is therefore fully bioavailable upon instillation. The two essential attributes of a dialysis solution, solute clearance and ultrafiltration (fluid removal), commence immediately upon administration, as the diffusive and osmotic pressure gradients are established once the solution is present in the peritoneal cavity.

Icodextrin contained in Extraneal acts as a colloid osmotic agent to achieve ultrafiltration across the peritoneal membrane. Extraneal is able to effect ultrafiltration while remaining essentially isosmolar with respect to plasma (~285 mOsm/L), in contrast to glucose-containing solutions, which act by crystalloid osmosis and are hyperosmolar (346 to 485 mOsm/L). Because of its high molecular weight, icodextrin is absorbed from the peritoneal cavity much slower than glucose. As a result, Extraneal is able to achieve sustained ultrafiltration during long peritoneal dialysis dwells.

The absorption of icodextrin occurs primarily by convective uptake from the peritoneal cavity via the peritoneal lymphatics. Absorbed icodextrin is metabolized by circulating α-amylase to smaller glucose polymers with a degree of polymerization (DP) less than that of the original polymer. These polymers are further metabolized to small oligosaccharides, principally maltose (DP2), maltotriose (DP3) and maltotetraose (DP4). Maltose is ultimately metabolized by maltase to glucose. The metabolism of icodextrin is shown in **Figure 4A**.

Figure 4A: Metabolism of Icodextrin



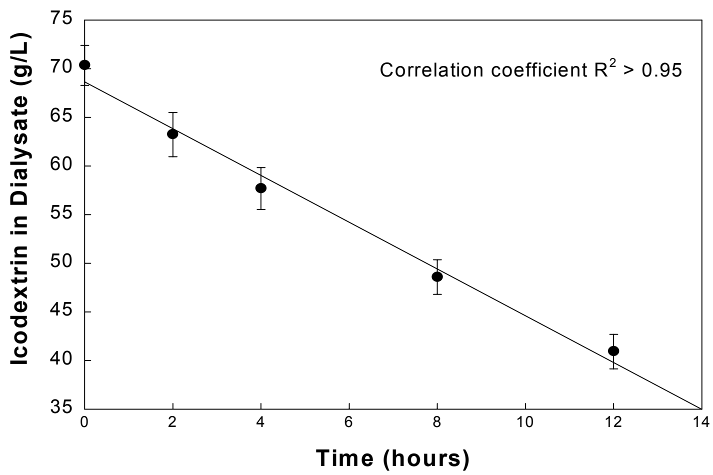
Although glucose is the ultimate metabolite of icodextrin, in contrast to dextrose-based solutions, Extraneal did not increase blood glucose levels or result in an insulinemic response in the single-dose pharmacokinetic study (RD-99-CA-060).

4.1 Single-Dose Pharmacokinetics

Single-dose pharmacokinetic parameters of Extraneal were evaluated in a single study (**RD-99-CA-060**) involving 13 ESRD patients treated with CAPD. The study evaluated the absorption kinetics of icodextrin from the peritoneal cavity and its elimination from blood after a single, 12-hour dwell. Blood levels of icodextrin and metabolites were monitored in plasma, dialysate and urine. Blood levels of icodextrin are defined as the sum of all polymers with a degree of polymerization (DP) greater than or equal to maltose (DP2) and were quantified by total hydrolysis of icodextrin to glucose, followed by enzymatic determination of glucose. Icodextrin metabolites, including maltose (DP2), maltotriose (DP3), maltotetraose (DP4), maltopentaose (DP5), maltohexaose (DP6) and maltoheptaose (DP7), were individually quantified using high performance anion-exchange chromatography with pulsed amperometric detection (HPAE-PAD).

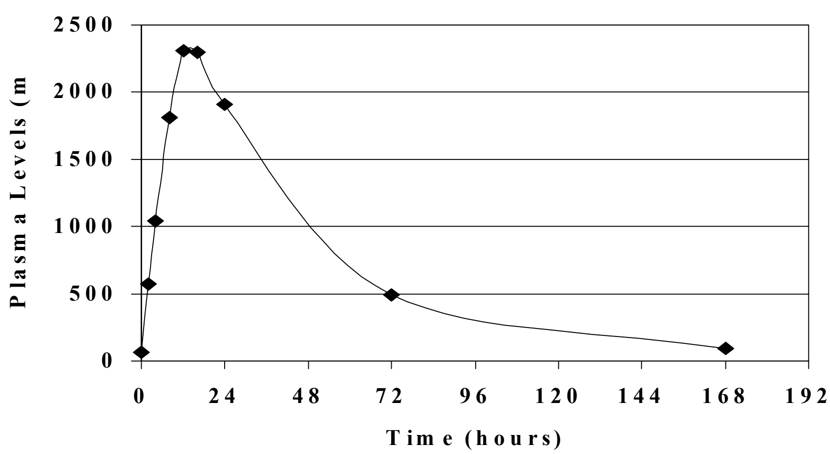
The absorption of icodextrin was evaluated by monitoring the disappearance of icodextrin from the peritoneal cavity after instillation of the dialysis solution (**Figure 4B**). Absorption of icodextrin from the peritoneal cavity followed zero-order kinetics consistent with convective transport via peritoneal lymphatic pathways. A median of 40.1% (60.2 g) of the administered dose was absorbed during the 12-hour dwell (range 36.29 to 102.37 g). These results are consistent with the absorption of icodextrin via the peritoneal lymphatics.

Figure 4B: Mean Concentration of Icodextrin in the Peritoneal Cavity



Plasma levels of icodextrin rose during the dwell and declined after draining from the peritoneal cavity (**Figure 4C**). Plasma kinetics fit a one-compartment model with zero-order absorption and first-order elimination. Peak plasma concentrations (median C_{peak} = 2.23 g/L) were observed at the end of the long dwell exchange (median T_{max} = 12.7 hours) with plasma levels returning to baseline values within 3 to 7 days following the single dose.

Figure 4C: Mean Plasma Icodextrin versus Time

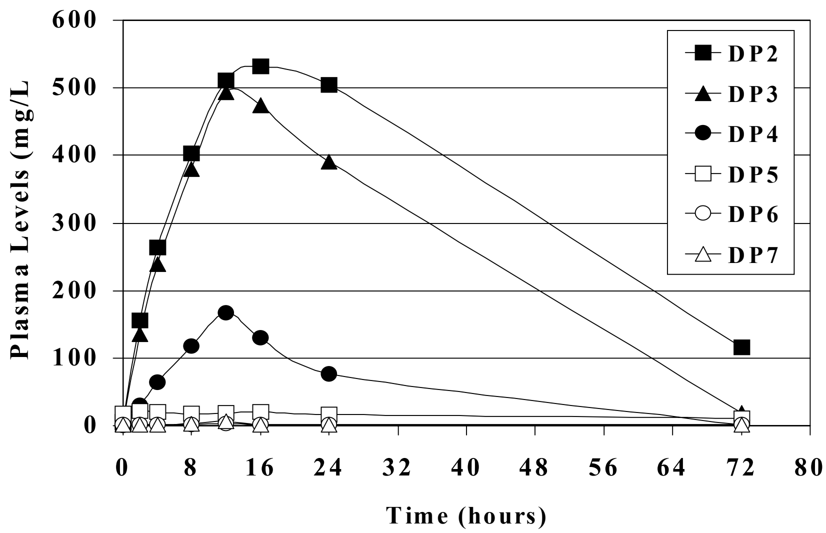


Icodextrin had a plasma half-life of 14.7 hours (range 10.88 to 21.27 hrs) and a median clearance rate of 1.09 L/hr (range 0.55 to 2.28 L/hr). The median distribution volume was

22.73 L (range 11.28 to 40.43 L), and the AUC calculated by the trapezoidal method had a median of 153.69 g/L/hr (range 55.13 to 180.60).

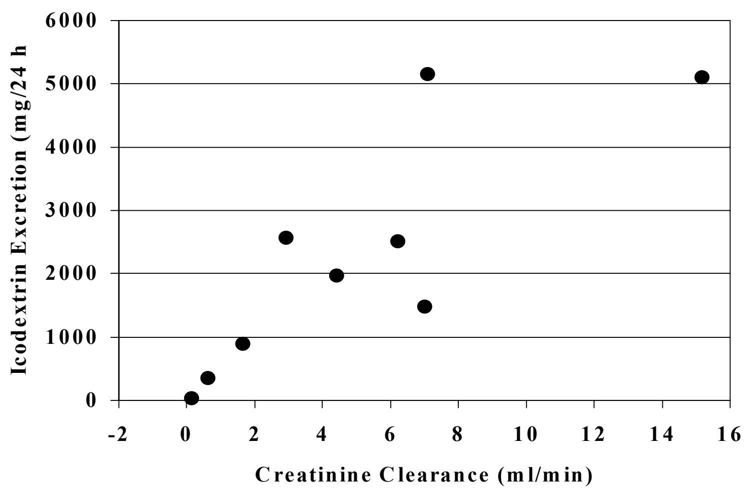
Plasma levels of icodextrin metabolites maltose (DP2), maltotriose (DP3) and maltotetraose (DP4) increased following Extraneal administration with a profile similar to that of total icodextrin (**Figure 4D**). Peak values were achieved following the end of the dwell and declined to baseline levels by 3 to 7 days. Only very small increases in blood levels of larger metabolites (DP5 to DP7) were observed.

Figure 4D: Mean Plasma Levels of Icodextrin Metabolites



Icodextrin and metabolites were cleared by urinary excretion and dialysis as well as metabolism to glucose. Urinary excretion of icodextrin was directly proportional to the level of residual renal function (r=0.824 vs. creatinine clearance, $p<0.01$) (**Figure 4E**). In the nine patients with residual renal function (mean creatinine clearance: 5.0 ± 1.5 ml/min), the average daily urinary excretion of icodextrin was 473 ± 77 mg per ml of creatinine clearance.

Figure 4E: Correlation Between Urinary Icodextrin Excretion and Creatinine Clearance



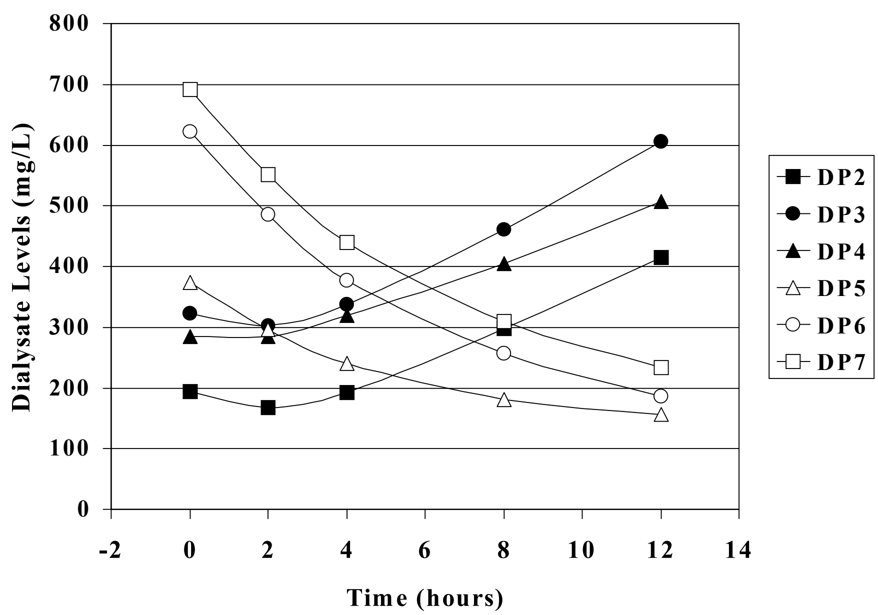
Elimination of the smaller icodextrin metabolites by dialysis was evident during the subsequent dialysis exchanges (following the Extraneal exchange), particularly for DP2 and DP3 (**Table 4A**). Recoveries of icodextrin in the subsequent first and second exchanges may also result from the icodextrin present in the residual fluid in the peritoneal cavity after drainage of the initial dwell. In the third subsequent exchange, essentially all of the icodextrin present in the dialysate is contributed by the metabolites DP2 to DP4.

Table 4A: Concentration of Icodextrin and Metabolites DP2-DP4 in Dialysate from the Three Exchanges after the Single 12-hour Exchange

Icodextrin or Metabolites	Concentration (g/L)		
	1st exchange	2nd exchange	3rd exchange
DP2	0.27 ± 0.031	0.29 ± 0.039	0.24 ± 0.024
DP3	0.26 ± 0.034	0.25 ± 0.035	0.18 ± 0.021
DP4	0.12 ± 0.017	0.075 ± 0.011	0.039 ± 0.007
Sum of DP2-DP4	0.65	0.62	0.46
Icodextrin	3.41 ± 0.55	0.85 ± 0.11	0.47 ± 0.05

Some intraperitoneal metabolism of icodextrin also occurred based on an observed increase in the concentration of the smaller polymers in the dialysate during the 12-hour dwell (**Figure 4F**). During the dwell, the concentrations of smaller polymers (DP2 – DP4) increased while those of the larger polymers declined (DP5 – DP7), indicating metabolism. The rise in the dialysate concentrations of the smaller metabolites (DP3 and DP4) is unlikely to be due to diffusion from the systemic circulation after extraperitoneal metabolism, as the concentrations in the peritoneal fluid remain higher than the circulating levels of these two metabolites for most of the dwell period. In the case of maltose (DP2), the plasma concentration exceeds the dialysate concentrations by the 4th hour of the dwell and remains higher for the remainder of the 12-hour dwell. Therefore, the rise in dialysate concentration could be the result of either intraperitoneal production or back diffusion from the systemic circulation (i.e., dialysis) or both.

Figure 4F: Evidence for Intraperitoneal Metabolism of Icodextrin During the Extraneal Dwell

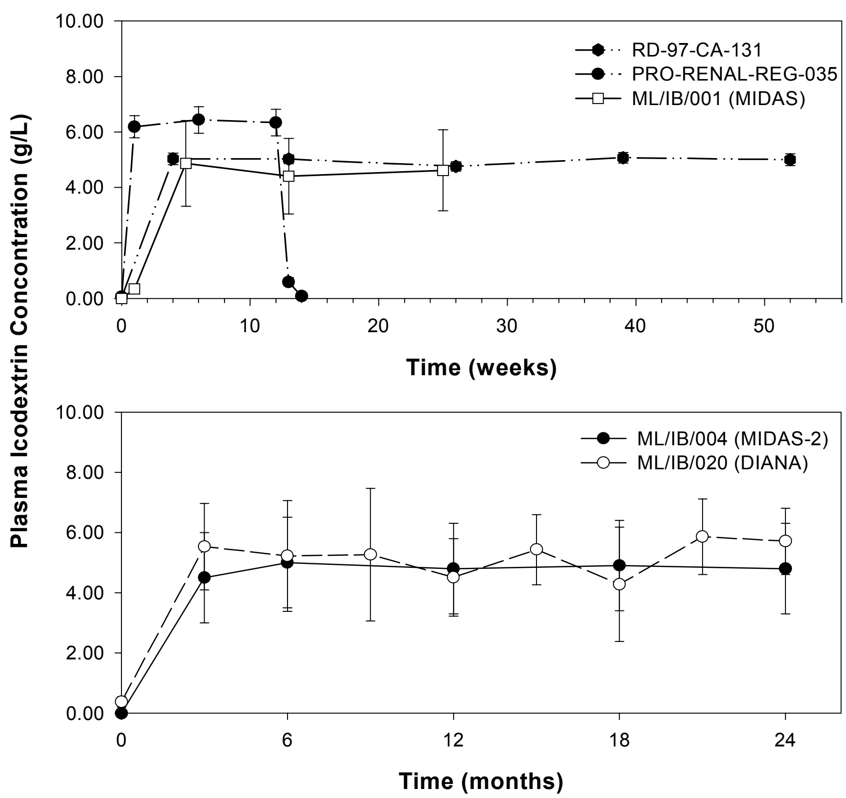


Single-dose pharmacokinetics closely predicted steady-state blood levels observed during multiple-dose studies. Using kinetic values obtained from each patient in the single dwell study, the predicted mean steady-state plasma concentration of total icodextrin was 5262 ± 461 (SE) mg/L. This compares closely to mean steady-state plasma concentrations for icodextrin observed during long-term administration of Extraneal.

4.2 Multiple-Dose Pharamcokinetics

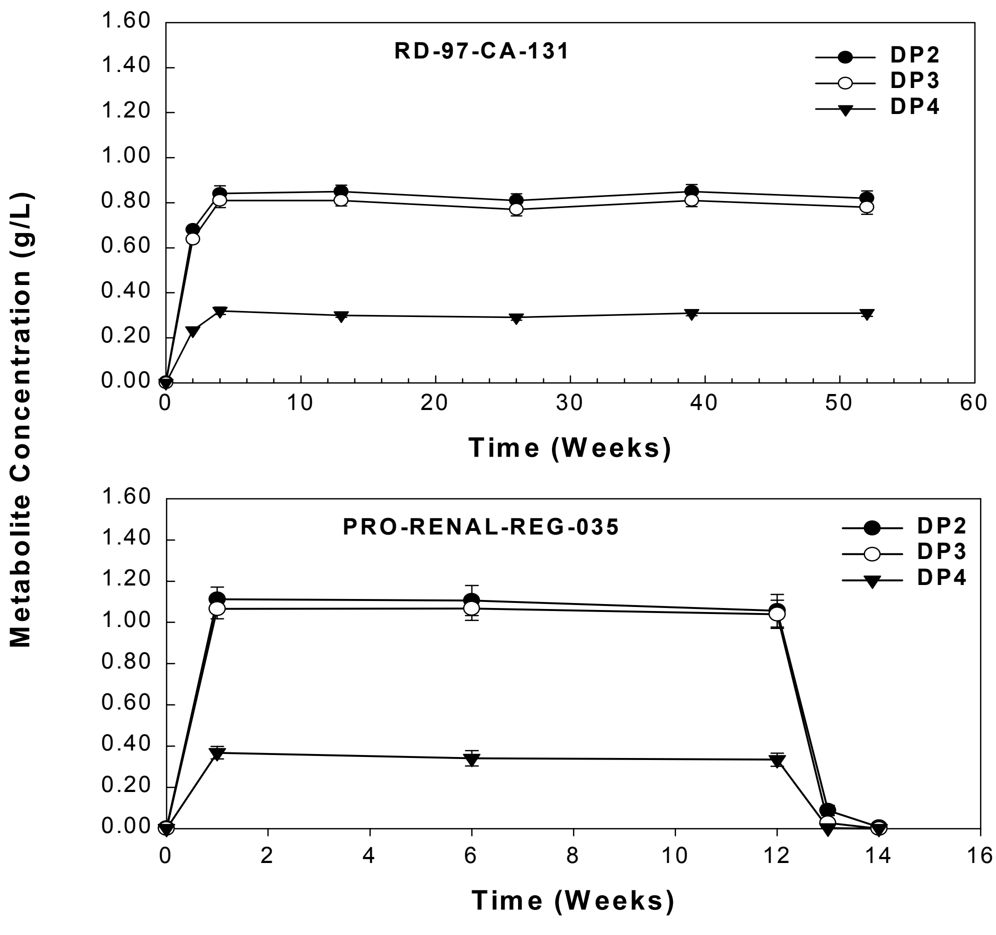
In multiple-dose studies, approximately 20% to 40% of the administered icodextrin was absorbed from the peritoneal cavity, depending on the duration of the dwell. Steady-state levels of icodextrin and metabolites were achieved within approximately one week and remained at a consistent level throughout the duration of exposure for at least two years (**Figure 4G**). Steady-state plasma concentrations of icodextrin ranged from 4 to 6.5 g/L and were consistent within and among studies. Small differences in the steady-state blood concentrations may be attributed to differences in dwell times, infusion volumes and sampling times (i.e., before or after the long dwell with Extraneal). In the study with available follow-up data on blood levels (PRO-RENAL-REG-035), plasma icodextrin returned to baseline within approximately one week upon discontinuing use of Extraneal.

Figure 4G. Plasma Icodextrin Levels in Multiple-Dose Studies



Plasma steady-state concentrations of icodextrin metabolites in multiple-dose studies followed kinetics similar to icodextrin (**Figure 4H**). Steady-state levels of maltose (DP2) and other metabolites were achieved within approximately 1-2 weeks and remained constant for up to two years of Extraneal administration (range 0.81 to 1.35 g/L for maltose). Similar to results from the single dose study, maltose, maltotriose (DP3) and maltotetraose (DP4) were the primary metabolites observed in multidose studies. Steady-state plasma levels of DP5 – DP7 were not significantly different from baseline values.

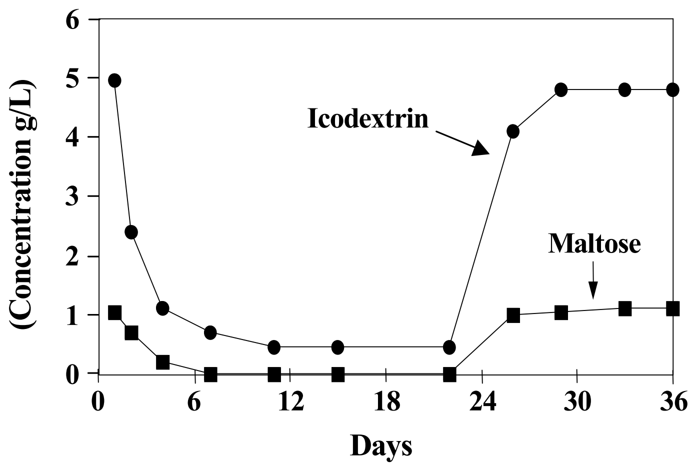
Figure 4H: Plasma Levels of Icodextrin Metabolites



In 12 CAPD patients treated with Extraneal for approximately 2 years (ML/IB/014; Steady-State Stop-Start Study, S-5), levels of icodextrin and maltose returned to baseline levels

within ~2 weeks following discontinuation of Extraneal.[6] Upon recommencing administration of Extraneal, levels of icodextrin and maltose returned to steady-state levels within ~1 week (**Figure 4I**). These results provide indirect evidence against any accumulation or tissue storage of icodextrin or metabolites during chronic administration.

Figure 4I: Kinetics of Icodextrin and Maltose Following Discontinuation and Readministration of Extraneal



In summary, icodextrin is bioavailable upon its instillation into the peritoneal cavity. In contrast to dextrose, the absorption of icodextrin from the peritoneal cavity is slow and allows for sustained ultrafiltration during a 12-16 hour dwell. Disappearance of icodextrin from the peritoneal cavity follows zero order kinetics, consistent with uptake via the lymphatics. The total amount of icodextrin absorbed depends on the dwell time and averages 30 - 40% of the administered dose.

Absorbed icodextrin is metabolized by α-amylase into smaller oligosaccharides, particularly maltose, maltotriose and maltotetraose. Following a single dose, peak plasma levels of icodextrin and its metabolites are obtained at the end of the dwell and decline thereafter, reaching baseline within three to seven days. During repeated daily administration of Extraneal, plasma levels of icodextrin and metabolites attain steady-state concentrations within approximately 1-2 weeks and remain constant during chronic exposure. Steady-state levels of icodextrin, including metabolites, range from ~4.5 to 6.0 g/L, of which ~1.0 g/L is contributed by the maltose and an equal amount by maltotriose. Some metabolism of icodextrin also occurs in the peritoneal cavity during the dwell. In contrast to dextrose-based solutions, absorption of icodextrin did not result in glycemia or an insulinemic response in the single dose pharmacokinetic study.

Plasma kinetics of icodextrin can be modeled using a one-compartment model with zero order absorption and first order elimination. Kinetic parameters obtained from a single dose study closely predict steady-state values obtained in multidose studies. Levels of icodextrin and metabolites return to baseline values within approximately one to two weeks after discontinuation of Extraneal, regardless of the duration of exposure (i.e., even following two years of daily administration). Readministration of Extraneal results in a return to steady-state levels similar to previous steady-state levels, with no evidence of a rebound effect. These findings suggest that icodextrin and metabolites are readily eliminated from the body and do not accumulate in a deep body pool.

Renal excretion of icodextrin and metabolites occurs in patients with residual renal function, and excretion rates are directly correlated with renal creatinine or urea clearances. Elimination of metabolites from the blood into the dialysate occurs during subsequent exchanges for the metabolites maltose and maltotriose.

5.0 EFFICACY

5.1 Introduction

The efficacy of Extraneal was compared with dextrose solutions during long daily dwells of 8 to 16 hours in three key studies, ML/IB/001 (MIDAS), RD-97-CA-130, and PRO-RENAL-REG-035.

The primary efficacy parameter was net UF. Secondary efficacy parameters were peritoneal creatinine clearance and peritoneal urea nitrogen or urea clearances (Studies RD-97-CA-130 and PRO-RENAL-REG-035). The efficacy results for the three key studies are presented separately by study due to differences in dialysis method (CAPD vs. APD), control dextrose concentration, dwell time, and time points of assessments. These different assessments yielded six efficacy comparisons for the three key studies which are summarized in **Table 5A**.

Table 5A: Efficacy Comparisons in Key Studies

Study	Dialysis Method	Dextrose versus Extraneal Concentration and Dwell Time	Time Points
ML/IB/001 (MIDAS)	CAPD	1.5% dextrose versus Extraneal, 8-hour dwell	Baseline, weeks 3, 12, and 20
		1.5% dextrose versus Extraneal, 12-hour dwell	Baseline, weeks 4, 13, and 21
		2.5/4.25% dextrose versus Extraneal, 8-hour dwell	Baseline, weeks 3, 12, and 20
		2.5/4.25% dextrose versus Extraneal, 12-hour dwell	Baseline, weeks 4, 13, and 21
RD-97-CA-130	CAPD	2.5% dextrose versus Extraneal, 12 ± 4-hour dwell	Baseline, weeks 2 and 4
PRO-RENAL-REG-035	APD	2.5% dextrose versus Extraneal, 14 ± 2-hour dwell	Baseline, weeks 1, 6, and 12

5.2 Methodology for Efficacy Evaluations

5.2.1 Primary Efficacy Evaluations

Net UF is measured by subtracting the fill volume of the infused solution from the drain volume obtained at the end of the long dwell period. The fill volume is the volume (mL) of peritoneal dialysis solution in the solution container prior to infusion. The drain volume is measured by weighing (g) the total amount of fluid collected at the end of the dwell. Each mL of fluid was assumed to weigh 1 gram.

5.2.2 Secondary Efficacy Evaluations

Peritoneal creatinine and urea nitrogen or urea clearances for the long dwell exchange were measured by obtaining the appropriate dialysate and blood samples. Clearances were calculated using standard formulae.

Clearances were calculated as follows:

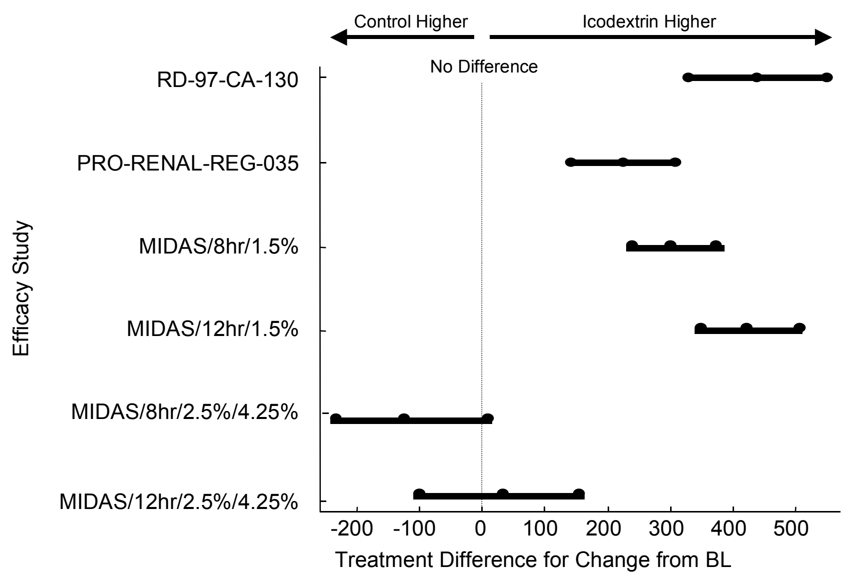
$$\frac{\text{Dialysate concentration (urea nitrogen, urea, or creatinine) X Drain volume / Dwell time}}{\text{Plasma concentration (urea nitrogen, urea, or creatinine)}}$$

5.3 Results for Primary Efficacy Endpoints

5.3.1 Net Ultrafiltration (UF)

Significant increases in fluid removal were achieved during the long dwell in patients in the Extraneal group compared to patients in the Control group for both 1.5% and 2.5% dextrose. The mean change from baseline for net UF was greater in the Extraneal group compared to the Control group for both 1.5% and 2.5% dextrose, and was comparable to 4.25% dextrose for the 12-hour dwell (**Figure 5A**).

Figure 5A: Treatment Group Differences (90% Confidence Intervals) for Net UF from Each Efficacy Study

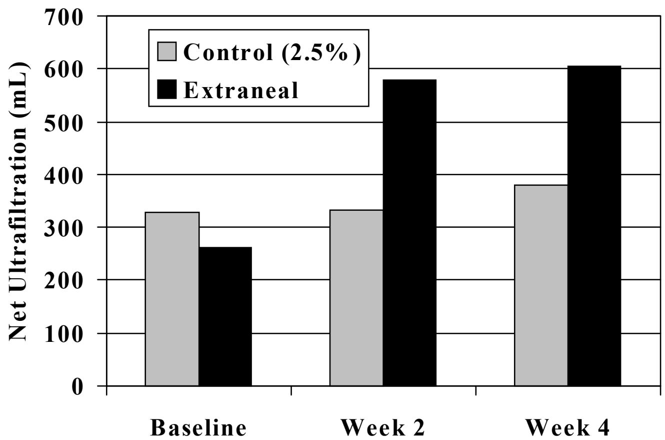


5.3.1.1 Results by treatment arm and dwell time

RD-97-CA-130: Mean Net UF for 12-hour Dwell

As displayed in **Figure 5B**, mean net UF was increased in the Extraneal group compared with the 2.5% dextrose group at both the week 2 and week 4 visits. Analysis of covariance revealed that the mean changes in UF were significantly higher in the Extraneal group compared with the 2.5% dextrose group at both weeks 2 ($p=0.008$) and 4 ($p<0.001$).

Figure 5B: Study RD-97-CA-130; Mean UF in 2.5% Dextrose-Treated Patients Versus Extraneal-Treated Patients for the 12 ± 4-hour Dwell

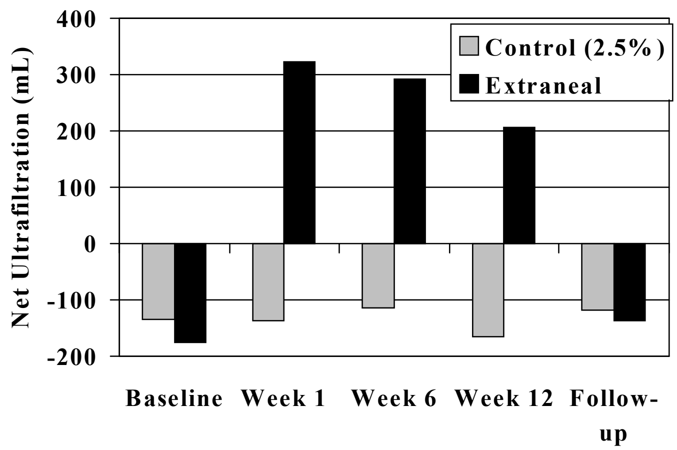


PRO-RENAL-REG-035 (APD): Mean Net UF for 14-hour Dwells

At baseline, both groups had a negative mean net UF during the long dwell (**Figure 5C**). Within the first week the mean net UF was increased in the Extraneal group to a positive net UF (323 mL versus -136 mL). Similar results were obtained at weeks 6 (292 mL versus -115 mL) and 12 (206 mL versus -165 mL).

Analysis of covariance revealed that the mean changes in net UF from baseline were significantly higher in the Extraneal compared with the 2.5% dextrose groups at weeks 1, 6, and 12 ($p<0.001$ at all 3 visits).

Figure 5C: Study PRO-RENAL-REG-035; Mean UF in 2.5% Dextrose-Treated Patients Versus Extraneal-Treated Patients for the 14 ± 2-hour Dwell



MIDAS ML/IB/001: Mean Net UF During 12-hour Dwells

In the open label MIDAS study, patients were randomized to 7.5% icodextrin, "weak dextrose, 1.5%" or "strong dextrose, 2.5%, 3.5% or 4.25%". The specific strong dextrose solution used was determined by patient fluid management requirements and may have varied during the course of the study. At study weeks 4, 13 and 21, ultrafiltration was measured for a 12-hour dwell, and the strong dextrose concentration recorded. The number of dwells measured at weeks 4, 13 and 21 are shown below by dextrose concentration.

Solution	Number of 12-hour dwells reported
7.5% Icodextrin	1,231
"Weak dextrose" (1.5%)	747
"Strong dextrose" (2.5%)	24
"Strong dextrose" (3.5%)	7
"Strong dextrose" (4.25%)	556
Total "Strong dextrose"	587

Figure 5D presents the comparison of mean net UF for the Extraneal group and the 1.5% dextrose group at all time points for the 12-hour dwell. Analysis of covariance revealed that the mean changes in UF were significantly greater in the Extraneal group compared with the 1.5% dextrose group (p<0.001 at all 3 visits).

Figure 5D: Study ML/IB/001 (MIDAS); Mean UF in 1.5% Dextrose-Treated Patients versus Extraneal-Treated Patients for the 12-hour Dwell

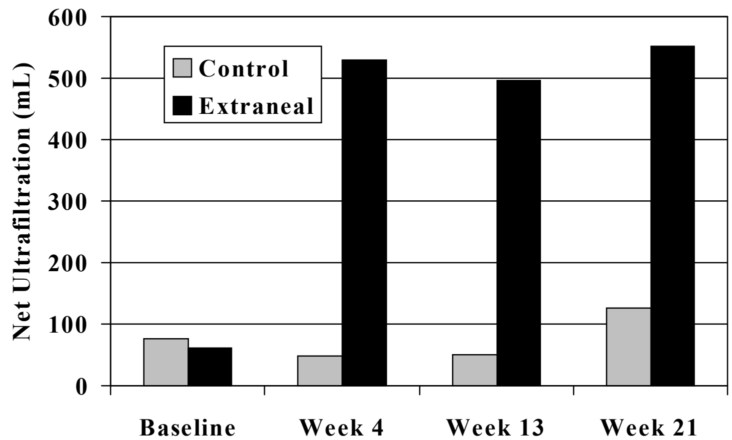
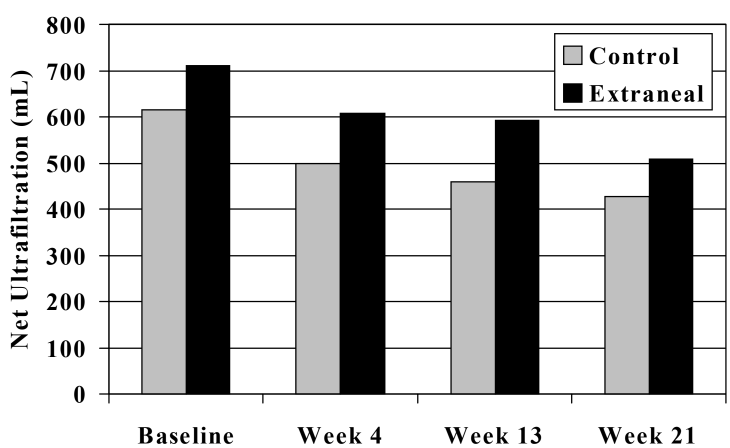


Figure 5E presents the comparison between the Extraneal group compared with the 2.5/4.25% dextrose group at all time points for 12-hour dwells. Although the net UF was greater in the Extraneal group compared with the high dextrose group, analysis of covariance revealed that the mean changes in UF were not significantly different between the 2 treatment groups at weeks 4, 13 and 21.

Figure 5E: Study ML/IB/001 (MIDAS); Mean UF in 2.5/4.25% Dextrose-Treated Patients versus Extraneal-Treated Patients for the 12-hour Dwell



MIDAS ML/IB/001: Mean Net UF During 8-hour Dwells

In parallel with the controlled collections of 12-hour dwells during weeks 4, 13, and 21, patients were asked to also collect long dwells on their usual overnight exchanges. These measurements were determined on weeks 3, 12, and 20. These measurements were reflective of real life long dwells and the majority ranged from 7 to 11 hours. These collections have been referred to as "8-hour" dwells following the standard terminology in the medical field of describing overnight exchanges as consisting usually of 8 hours.

In the "strong dextrose" group, approximately 3.3% of the dwells were using 2.5% dextrose. The remaining "strong dextrose" dwells were performed with 4.25% dextrose.

Figure 5F presents the comparison of mean net UF for the Extraneal group and the 1.5% dextrose group at all time points for the 8-hour dwell. Analysis of covariance revealed that the mean changes in UF were significantly greater in the Extraneal group compared with the 1.5% dextrose group at weeks 3, 12, and 20 ($p<0.001$ at all three visits).

Figure 5F: Study ML/IB/001 (MIDAS); Mean UF in 1.5% Dextrose-Treated Patients versus Extraneal-Treated Patients for the 8-hour Dwell

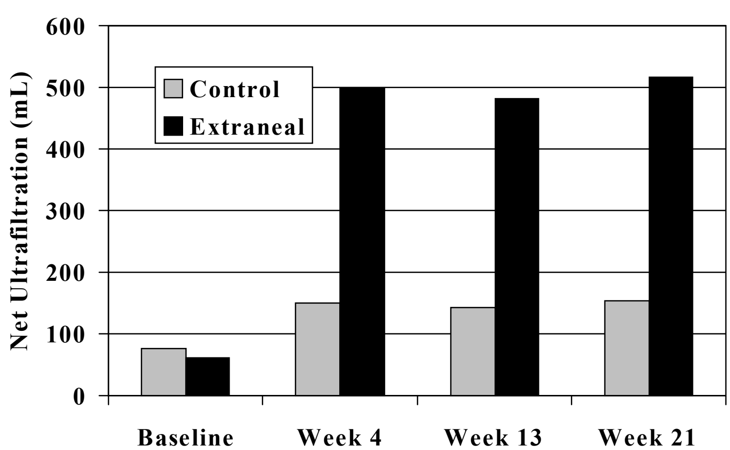
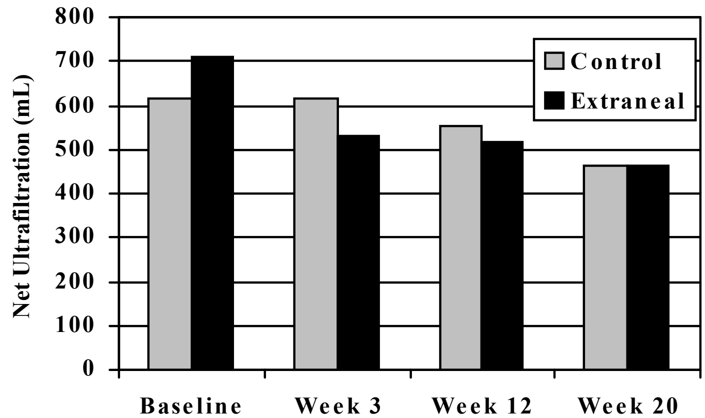


Figure 5G presents the comparison of mean net UF for the Extraneal group and the 2.5/4.25% dextrose group at all time points for the 8-hour dwell. Analysis of covariance revealed that the mean changes in net UF between the Extraneal and the 2.5/4.25% dextrose treatment groups were significantly different at week 3 ($p=0.011$), but not significantly different at weeks 12 ($p=0.246$) and 20 ($p=0.372$).

Figure 5G: Study ML/IB/001 (MIDAS); Mean UF in 2.5/4.25% Dextrose-Treated Patients versus Extraneal-Treated Patients for the 8-hour Dwell



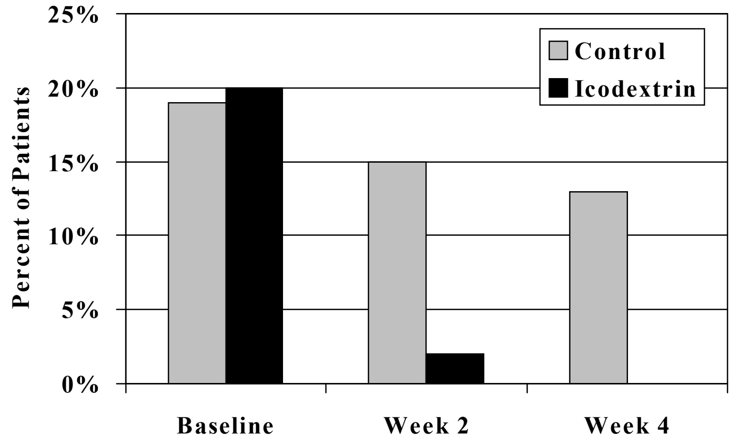
5.3.1.2 Patients With Negative Net UF for the Long Dwell Exchange

An alternate way of examining efficacy of a solution during the long dwell is to determine the proportion of patients experiencing negative net ultrafiltration defined as a drain volume numerically smaller than the instilled volume.

RD-97-CA-130: Percentage of Patients who have Negative Net UF

The percentage of patients with negative net ultrafiltration was significantly reduced in the Extraneal group compared with the 2.5% dextrose group at weeks 2 (p=0.004) and 4 (p<0.001) (**Figure 5H**).

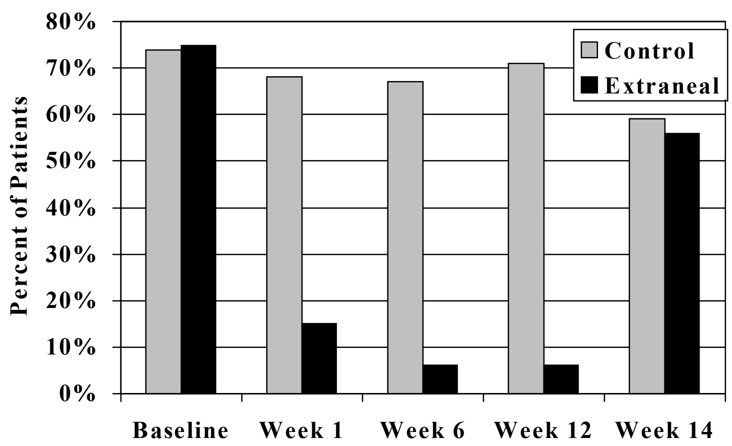
Figure 5H: RD-97-CA-130; Percentage of Patients who have Negative Net UF for the 12 ± 4 hour Dwell (2.5% Dextrose versus Extraneal)



PRO-RENAL-REG-035: Percentage of Patients who have Negative Net UF

The percentage of patients who have negative net UF was significantly reduced in the Extraneal group compared with the 2.5% dextrose group at all time points (p<0.001) (**Figure 5I**).

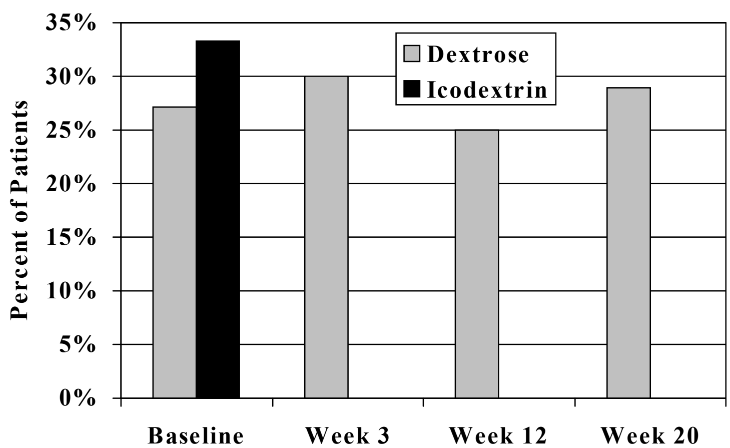
Figure 5I: PRO-RENAL-REG-035: Percentage of Patients who have Negative Net UF for the 14 ± 2-hour Dwell (2.5% Dextrose versus Extraneal)



ML/IB/001 (MIDAS): Percentage of Patients with Negative UF in MIDAS Study for 8- and 12-hour Dwells

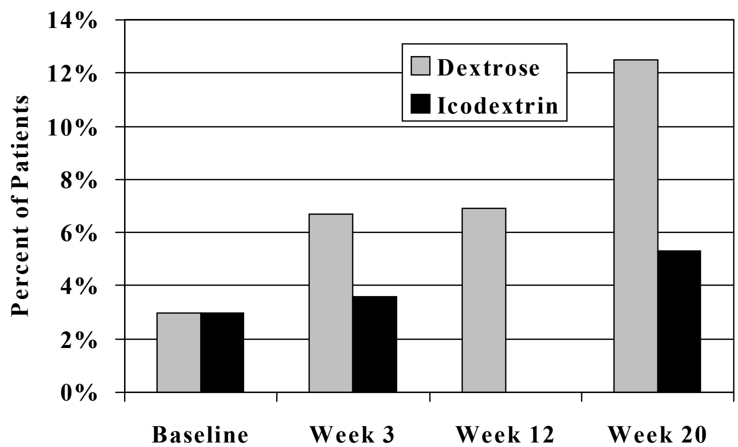
For the 8-hour dwells, the percentage of patients with negative net UF was significantly reduced in the Extraneal group compared with the 1.5% dextrose group at all time points ($p<0.001$) (**Figure 5J**).

Figure 5J: ML/IB/001 (MIDAS); Percentage of Patients with Negative Net UF for the 8-hour Dwell (1.5% Dextrose versus Extraneal)



The percentage of patients with negative net UF at Baseline was 3% in both the Extraneal and the 2.5/4.25% dextrose treatment groups **(Figure 5K)**. Although the percentage of patients with negative net UF was lower in the Extraneal group than in the 2.5/4.25% dextrose group, the reduction was not statistically significant.

Figure 5K: ML/IB/001 (MIDAS); Percentage of Patients with Negative Net UF for the 8-hour Dwell (2.5/4.25% Dextrose versus Extraneal)



For the 12-hour dwell, the percentage of patients with negative net UF was significantly reduced in the Extraneal group compared with the 1.5% dextrose group at weeks 4 (5% versus 31%; p=0.001), 13 (3% versus 39%; p<0.001), and 21 (0% versus 26%, p=0.001) **(Figure 5L)**.

Figure 5L: ML/IB/001 (MIDAS); Percentage of Patients with Negative Net UF in the 12-hr dwell (1.5% Dextrose versus Extraneal)

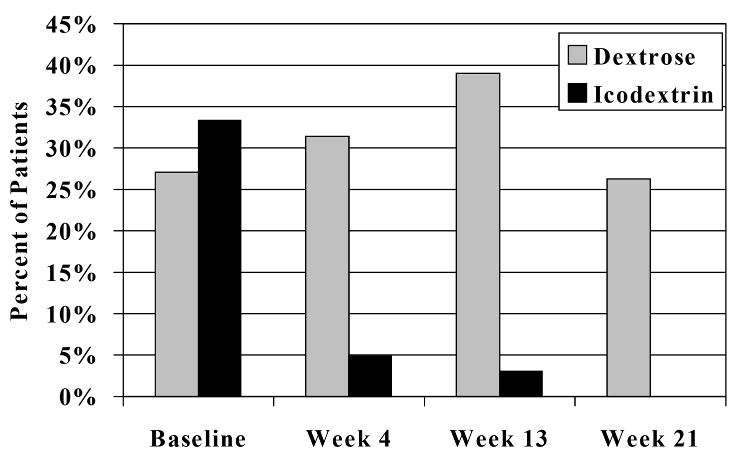
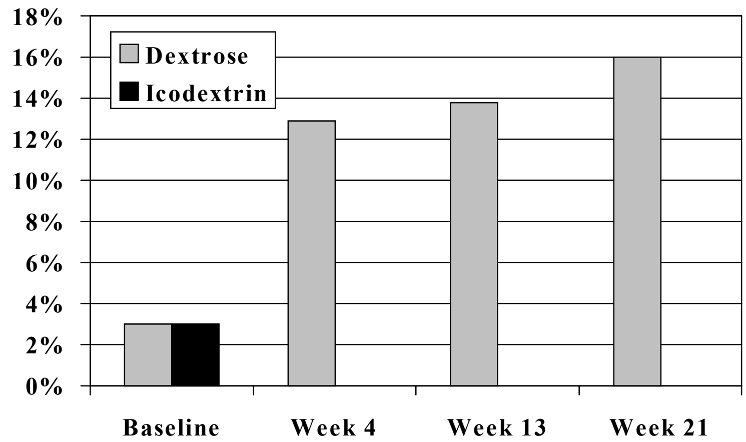


Figure 5M illustrates the percentage of patients with negative net UF at Baseline, and weeks 4, 13, and 21 in the 2.5/4.25% dextrose arm of ML/IB/001 (MIDAS) for the 12-hour dwell. Although the percentage of patients with negative net UF was reduced in the Extraneal group compared with 2.5/4.25% dextrose group at weeks 4, 13, and 21, this reduction was not statistically significant.

Figure 5M: ML/IB/001 (MIDAS); Percentage of Patients with Negative Net UF (2.5/4.25% Dextrose versus Extraneal)



5.4 Results for Secondary Efficacy Endpoints

These evaluations were completed using the 2.5% dextrose active treatment as a comparator.

5.4.1 Creatinine Clearance for the Long Dwell Exchange

Creatinine clearance was significantly greater for Extraneal than the dextrose based solution during the long dwell exchange **(Table 5B).**

Table 5B: Mean and Mean Change From Baseline for Peritoneal CreatinineClearance (mL/min)

	RD-97-CA-130		PRO-RENAL-REG-035	
	2.5% Dextrose	Extraneal	2.5% Dextrose	Extraneal
Week 1 (14±2-hr Dwell)				
N			19	20
Mean ± SEM			2.19 ± 0.14	2.55 ± 0.10*
Mean Change ± SEM			0.10 ± 0.15	0.45 ± 0.07*
Week 2 (12±4-hr Dwell)				
N	82	84		
Mean ± SEM	3.44 ± 0.11	4.09 ± 0.12*		
Mean Change ± SEM	0.01 ± 0.12	0.64 ± 0.11*		
Week 4 (12±4-hr Dwell)				
N	81	81		
Mean ± SEM	3.51 ± 0.13	4.00 ± 0.10*		
Mean Change ± SEM	0.10 ± 0.13	0.56 ± 0.08*		
Week 6 (14±2-hr Dwell)				
N			18	17
Mean ± SEM			2.20 ± 0.13	2.66 ± 0.12*
Mean Change ± SEM			0.00 ± 0.06	0.58 ± 0.11*
Week 12 (14±2-hr Dwell)				
N			17	17
Mean ± SEM			2.10 ± 0.11	2.54 ± 0.09*
Mean Change ± SEM			0.05 ± 0.08	0.46 ± 0.08*

* p<0.05 vs. dextrose

5.4.2 Urea Nitrogen and Urea Clearances for the Long Dwell Exchange

Urea nitrogen clearance and urea clearance were significantly greater for Extraneal than the dextrose based solution during the long dwell exchange **(Table 5C).**

Table 5C: Mean and Mean Change From Baseline for Peritoneal Urea Nitrogen and Urea Clearances (mL/min)

	RD-97-CA-130**		PRO-RENAL-REG-035**	
	2.5% Dextrose	Extraneal	2.5% Dextrose	Extraneal
Week 1 (14±2-hr Dwell)				
N			19	20
Mean ± SEM			2.28 ± 0.14	2.62 ± 0.10*
Mean Change ± SEM			0.07 ± 0.15	0.45 ± 0.08*
Week 2 (12±4-hr Dwell)				
N	82	84		
Mean	4.12 ± 0.13	4.56 ± 0.11*		
Mean Change ± SEM	-0.06 ± 0.13	0.34 ± 0.11*		
Week 4 (12±4-hr Dwell)				
N	82	80		
Mean	4.12 ± 0.13	4.53 ± 0.11*		
Mean Change ± SEM	-0.04 ± 0.11	0.31 ± 0.09*		
Week 6 (14±2-hr Dwell)				
N			18	17
Mean			2.34 ± 0.15	2.74 ± 0.12*
Mean Change ± SEM			0.01 ± 0.07	0.59 ± 0.11*
Week 12 (14±2-hr Dwell)				
N			17	17
Mean			2.27 ± 0.14	2.63 ± 0.09*
Mean Change ± SEM			-0.01 ± 0.09	0.47 ± 0.09*

** Peritoneal urea nitrogen clearance was measured in RD-97-CA-130 and peritoneal urea clearance was measured in PRO-RENAL-REG-035.

* $p<0.05$ vs. dextrose

5.5 Overall Efficacy Conclusion

Results of the three key studies demonstrate that net UF was significantly greater in patients treated with Extraneal compared with the 1.5% or 2.5% dextrose solutions for long peritoneal dialysis dwell times up to 16 hours. In the MIDAS study, which evaluated 4.25% dextrose, net UF was comparable between patients treated with Extraneal and 4.25% dextrose solution.

The number of patients who experienced negative net UF was significantly reduced in Extraneal-treated patients compared with dextrose-treated patients.

The increased net UF observed with Extraneal compared with 1.5% or 2.5% dextrose was associated with significantly greater peritoneal clearance of creatinine and urea nitrogen or urea.

Subgroup analyses were conducted for age, gender, diabetes, hypertension, and race. The results for net UF and peritoneal creatinine, urea nitrogen and urea clearances for the subgroup analyses were comparable to those of the main population.

6.0 SAFETY

6.1 Safety Analysis Population

6.1.1 Clinical Studies Evaluating Safety

Four Key Clinical Studies and 5 Supportive Studies were used to evaluate the safety of Extraneal (**see Tables 6A and 6B**). A total of 840 (347 control and 493 Extraneal) patients were evaluable for safety, meaning that they received at least one dose of Extraneal or Control. A total of 197 patients are included more than once due to study design (crossover study, rollover extension, or substudy). Of the 840 total patients included in the safety analyses, 643 of these patients were unique patients (277 control, 366 Extraneal). However, medical events were counted per study, therefore the incidence rates are based upon patients exposed per study. All control groups were active controls on 1.5%, 2.5% or 4.25% dextrose solutions.

Studies were designated as “Key” or “Supportive”. Key studies were those considered to meet all of the requirements of adequate and well-controlled studies, per 21 CFR 314.126, intended to demonstrate efficacy and or safety for the proposed indication. Key studies for safety and efficacy are RD-97-CA-130, MIDAS (ML/IB001), PRO-RENAL-REG-035, and for safety RD-97-CA-131. Supportive studies were additional studies, which provide evidence for evaluation of the safety and or efficacy of Extraneal, but were intended to evaluate specific effects (e.g. pharmacokinetics, uncontrolled extension, etc.). Supportive studies included RD-99-CA-060, MIDAS-2 (ML/IB004), DIANA (ML/I011), MIDAS S-5 (ML/IB014), and DELIA (ML/IB009). The integrated database for safety included data from both the Key and supportive studies.

Safety analyses were conducted separately for the following subpopulations: patients with diabetes, patients with hypertension, and patients with a primary diagnosis of hypertensive nephropathy, as well as for demographic subpopulations by age, gender, and race. Unless described otherwise, all analyses presented were performed using the integrated database of all Key and Supportive studies.

A summary, by study, of the total safety population and patients contributed by each study is presented in **Table 6A**.

Table 6A: Safety Database Clinical Studies

Study	Control Group	Extraneal Group	Total Patients
Key Studies			
RD-97-CA-130	85	90	175
RD-97-CA-131	112	175	287
ML/IB/001 (MIDAS)	103	106	209
PRO-RENAL-REG-035	19	20	39
Total Key Studies	319	391	710
Supportive Studies			
ML/IB/011 (DIANA)	19	19	38
ML/IB/020 (DELIA)	9	10	19*
ML/IB/004 (MIDAS-2)	--	48	48
RD-99-CA-060	--	13	13
ML/IB/014 (S-5)	--	12	12
Total Supportive Studies	28	102	130
Total All Studies	**347**	**493**	**840**

*DELIA population data from Baxter. One patient received no drug and is not included in this table; 2 patients received icodextrin only; 1 received control only; a total of 12 patients were enrolled.

6.1.2 Safety Assessments

The following parameters were evaluated as described below:

- Peritoneal Equilibration Tests were performed to determine if any changes in the peritoneal membrane were taking place (RD-97-CA-130, RD-97-CA-131, Pro-Renal-Reg-035)
- Clinical laboratory tests were performed at baseline and at varying intervals depending on the study.
- Plasma was assayed for icodextrin and metabolites during the Key Studies.
- Evidence of fluid imbalance was evaluated by measuring changes in weight and by signs/symptoms of edema. These variables were recorded during the physical examination and/or as adverse events during Study RD-97-CA-131.
- Vital signs such as body weight were recorded at every study visit for all studies.
- In order to assess whether Extraneal had any impact on quality of life, as compared to Dextrose Solutions, the Kidney Disease Quality of Life (KDQoL) Questionnaire was administered during the long-term safety study, RD-97-CA-131.

- To evaluate effects of Extraneal on weight gain, observed in dextrose-based solutions, body weight was assessed as a secondary endpoint in long-term study RD-97-CA-131.
- Mortality assessment was planned for long-term study RD-97-CA-131, and evaluated across all controlled studies of Extraneal.

Safety measurements and timing of assessments for individual studies are described in **Table 6B**.

Table 6B: Clinical Safety Assessments of Extraneal in Patients with ESRD

Protocol Number	N	Study Design	Duration	AEs Reported Through	Safety[1] Labs	Icodextrin[2] and metabolites	Other Safety testing
Key Studies							
RD-97-CA-130	Total =175 I = 90 C = 85	Prospective, randomized, double-blind, and parallel group, active-controlled study comparing the efficacy and safety of Extraneal (7.5% icodextrin) with that of Dianeal for the overnight dwell in CAPD patients.	4 weeks	4 weeks with a 30-day follow-up post completion/ discontinuation	Baseline Week 4	Baseline Week 4	Peritoneal Equilbration Test (PET) baseline Chest X-ray was measured at Baseline only HbA1c collected at Baseline and Week 4 for diabetics only
RD-97-CA-131	Total = 287 I = 175 C = 112	Prospective, randomized, double blind, and parallel group, active-controlled study comparing the safety of Extraneal (7.5% icodextrin) with that if Dianeal for the long dwell in PD patients. Patients treated by both CAPD and APD were included.	52 weeks	52 weeks with a 30-day follow-up post completion/ termination-13 months from initiation for mortality.	Baseline Week 13 Week 26 Week 39 Week 52	Baseline Week 13 Week 26 Week 39 Week 52	PET at Baseline, weeks 26 and 52 Chest X-ray was measured at Baseline and week 52 HbA1c collected at Baseline, Weeks 13, 26, 29 and 52 for diabetics only
ML/IB/001	Total = 209 I = 106 C = 103	Open, randomized, active-controlled, parallel group study comparing the efficacy and safety of 7.5% Icodextrin with that of dextrose for the long overnight dwell in CAPD patients.	6 months	6 months	Baseline Visit 2 Visit 4 Visit 6 Visit 8 Visit 9 Visit 10 Visit 11 Visit 12	Baseline Visit 2 Visit 6* Visit 9* Visit 12	Chest X-ray, eye exam and ECG were measured at Baseline and Visits 2 and 12.

I = 7.5% icodextrin = Extraneal; C = control (Dianeal)
1 = Safety Labs include biochemistry, hematolgy with differential and platelets, and osmolality
2 = Icodextrin and metabolites were measured in plasma and dialysate. Icodextrin was only measured in dialysate for RD-97-CA-131. ML/IB/001 measured icodextrin and metabolites in plasma only
* = Plasma icodextrin (Dextrin 20) for weeks 6 and 9 were only measured in the Dextrin 20 group

Table 6B (continued): Clinical Safety Assessments of Extraneal in Patients with ESRD

Protocol Number	N	Study Description	Duration	AEs Reported Through	Safety[1] Labs Obtained at	Icodextrin[2] and metabolites Obtained at	Other Safety testing
Key Studies (continued)							
Pro-Renal-Reg-035	Total = 39 I = 20 C = 19	Open-label, randomized, parallel group, active-controlled study to compare the efficacy and safety of Extraneal 7.5% icodextrin with that of 2.27% glucose (Dianeal PD4) for the long daytime dwell in APD patients.	16 weeks	16 weeks	Visit –2 Visit -1 Visit 1 Visit 2 Visit 3 Visit 5	Visit –1 Visit 1 Visit 2 Visit 3 Visit 4 Visit 5	24 hour urine collection Baseline and Visit 3 PET at Visit –1 and 3 Diabetic diary collected at Baseline, Visit 1 and 2 HbA1c collected at baseline , visit 1, 2, 3 and 5 for diabetics only
Supportive Studies							
ML/IB/020	Total = 11 I = 11 7 patients completed both arms	Open, two-way crossover study to evaluate the safety, efficacy, and patient acceptability of Extraneal for the long (14-16- hour) dwell in APD patients.	6 weeks per treatment (4-week washout between)	20 weeks	Baseline Visit 2 Visit 3 Visit 4 Visit 5 Visit 6 Visit 7 Visit 8	Baseline[3] Visit 2 Visit 3 Visit 4 Visit 5 Visit 6 Visit 7 Visit 8	

I = 7.5% icodextrin = Extraneal; C = control (Dianeal)
1 = Safety Labs include biochemistry, hematology with differential and platelets, and osmolality including lipids for PRO-RENAL-REG-035
2 = Icodextrin and metabolites were measured in plasma and dialysate, dialysate was not collected at Week 4 for PRO-RENAL-REG-035. Icodextrin was only measured in dialysate for PRO-RENAL-REG-035
3 = Icodextrin was measured in the serum. Dialysate icodextrin was measured at Visit 4 and 7 only for ML/IB/020.

Table 6B (continued): Clinical Safety Assessments of Extraneal in Patients with ESRD

Protocol Number	N	Study Description	Duration	AEs Reported Through	Safety[1] Labs Obtained at	Icodextrin[2] and metabolites Obtained at	Other Safety testing
Supportive Studies (continued)							
ML/IB/011	Total = 38 I = 19 C = 19	Open-label, randomized, active-controlled, parallel group study comparing icodextrin with glucose for the long daytime dwell (12-16 hours) in APD patients in the Netherlands.	24 months	24 months	Baseline Visit 2 Visit 3 Visit 4 Visit 5 Visit 6 Visit 7 Visit 8 Visit 9	Baseline Visit 2 Visit 3 Visit 4 Visit 5 Visit 6 Visit 7 Visit 8 Visit 9	HbA1c collected at Visit 1, 2, 3, 4, 5, 6, 7, 8 and 9 for diabetics only Peritoneal Histology collected at Visit 1, 3, 5, 7 and 9 In vitro (effluent) collected to measure perioneal macrophage IL-1 production, Opsonin, IL-6, IL-8 TGF-β, TNF-α, CA-125, Procollagen, Glycated albumin at Visits 1, 2, 3, 4, 5, 6, 7, 8 and 9 Lipids collected at Visits 1, 3, 5, 7 and 9
ML/IB/004	Total = 48 I = 48	Open-label, long-term extension study to evaluate the safety of icodextrin in CAPD patients who have already received 6 months of therapy during the MIDAS study.	Varied; until treatment failure	As long as patient continued in trial	Every 3 months	Every 6 months	Eye examination at 6 month intervals
RD-99-CA-060	Total = 13 I = 13	Open, prospective, single exchange, pharmacokinetic study	Single, 12-hour dwell; patients followed for 28 days	28 days	Baseline Day 3 Day 7 Day 14 Day 28	Baseline[4] 2 hours 4 hours 8 hours 12 hours Day 3 Day 7 Day 14 Day 28	Dialysate sample and 24 hour Urine sample collected at baseline

I = 7.5% icodextrin = Extraneal™; C = control (Dianeal)
4= in addition to the collection after initial instillation of icodextrin, ten minutes after the first post study dwell is instilled and at the end of each dialysis exchange for all exchanges following the study dwell exchange for the first 24 hours of the study were collected.

Table 6B (continued): Clinical Safety Assessments of Extraneal in Patients with ESRD

Protocol Number	N	Study Description	Duration	AEs Reported Through	Safety[1] Labs Obtained at	Icodextrin and metabolites Obtained at	Other Safety testing
Supportive Studies (continued)							
ML/IB/014	Total = 12 12 patients received both treatments	Open, prospective pharmacokinetic study; sub-study of MIDAS-2; patients received dextrose solution	1 dwell/day for 3 weeks, then icodextrin solution 1 dwell/day for 2 weeks	5 weeks	Visit 1 Visit 3 Visit 4	Day 1[5] Day 3 Day 5 Day 8 Day 11 Day 15 Day 22 Day 26 Day 29 Day 33 Day 36	

I = 7.5% icodextrin = Extraneal™; C = control (Dianeal)
5 = dialysate samples were collected at Day 2, 3, 22-35 from the overnight dwell

6.1.1.1 Baseline Demographics and Clinical Characteristics

Baseline demographics for all studies are presented in **Table 6C**. Overall demographic characteristics were well balanced between the Extraneal and Control groups although there was a slightly higher percentage of males in the Extraneal group.

Table 6C: Baseline Demographics for Safety Population

	Control Group N = 347		Extraneal Group N = 493		All Patients N = 840	
Age (yrs)						
Mean ± SE	54.1± 0.76		53.9 ± 0.63		54.0 ± 0.48	
Range	19 – 86		18 – 83		18 - 86	
Weight (kgs)						
Mean ± SE	74.4 ± 0.82		75.6 ± 0.69		75.1 ±0.53	
Range	44.4 – 145.4		37.0 – 140.5		37.0 – 145.4	
	Control Group		**Extraneal Group**		**All Patients**	
	n	**%**	**n**	**%**	**n**	**%**
Gender						
Male	175	50.4	278	56.4	453	53.9
Female	172	49.6	215	43.6	387	46.1
Race						
Caucasian	257	74.1	360	73.0	617	73.5
Hispanic	10	2.9	14	2.8	24	2.9
Asian	12	3.5	22	4.5	34	4.0
Black	62	17.9	90	18.3	152	18.1
Other	6	1.7	7	1.4	13	1.5

Baseline clinical characteristics were similar for both groups (**Table 6D**). There were approximately 7% more patients described as hypertensive at baseline in the Extraneal group.

Table 6D: Baseline Clinical Characteristics

	Control Group N = 347		Extraneal Group N = 493		All Patients N = 840	
	n	%	n	%	n	%
Primary Renal Diagnosis						
Diabetic nephropathy	74	21.3	102	20.7	176	21.0
Hypertensive nephropathy	68	19.6	114	23.1	182	21.7
Glomerulonephritis	68	19.6	87	17.6	155	18.5
Polycystic kidney disease	22	6.3	28	5.7	50	6.0
Interstitial nephritis	11	3.2	23	4.7	34	4.0
Obstructive nephropathy	2	0.6	5	1.0	7	0.8
Autoimmune disease	9	2.6	7	1.4	16	1.9
Other	93	26.8	127	25.8	220	26.2
Diabetic						
Yes	94	27.1	132	26.8	226	26.9
No	244	70.3	350	71.0	594	70.7
Not recorded	9	2.6	11	2.2	20	2.4
Hypertensive*						
Yes	147	42.4	243	49.3	390	46.4
No	200	57.6	250	50.7	450	53.6
Hypertensive Nephropathy						
Yes	68	19.6	114	23.1	182	21.7
No	279	80.4	379	76.9	658	78.3

* Systolic pressure >140 mmHg and/or diastolic pressure >90 mmHg at baseline

Approximately one half of the patients identified as diabetic at baseline had the type of diabetes designated as Type I or Type II; the remaining diabetic patients did not have the type of diabetes described. Of those patients who were identified as having Type I or Type II diabetes, 12.2% more patients in the Extraneal group had Type I diabetes (Extraneal 35.6%, Control 23.4%).

6.1.1.2 Peritoneal Permeability Assessment

Peritoneal equilibration test (PET) was performed to assess membrane function at baseline and during three studies (RD-97-CA-130, RD-97-CA-131, PRO-RENAL-REG-034). There were no differences in mass transfer area coefficients for urea, creatinine, and glucose over the duration of these studies between Extraneal and the control group.

6.1.1.3 Extent of Exposure

The mean duration of exposure was longer in the Extraneal group (232.5 days compared to Control of 174.3 days) because the drug was studied in a greater number of patients in the two longer-term studies: MIDAS-2 (ML/IB/004) and RD-91-CA-131. MIDAS-2 was a long-term extension of MIDAS. Only patients receiving icodextrin were included in MIDAS-2. In RD-97-CA-131, 60% of patients were randomized to Extraneal for up to 12 months. **Table 6E** presents a summary of the duration of exposure to study drug for all studies.

Table 6E: Duration of Exposure For Clinical Studies

	Control Group		Icodextrin Group	
	N	Percent	N	Percent
Duration Categories (days)				
<30	78	22.5	103	20.9
30 - <90	51	14.7	75	15.2
90 - <180	93	26.8	100	20.3
180 - <360	50	14.4	60	12.2
>=360	75	21.6	155	31.4
TOTALS	347	100.0	493	100.0

6.1.1.4 Concomitant Medications-Key Studies

Use of concomitant medications was evaluated for the Key studies and the supportive study RD-99-CA-060 (pharmacokinetic study). The most commonly reported therapeutic class for both treatment groups was anti-anemic agents, used by 67.3% of Extraneal and 64.3% of Control patients.

At baseline, more patients randomized to Extraneal were using antithrombotic agents, antacids, beta blockers, renin-angiotensin system agents, and cardiac therapy. More control patients were using agents identified as “unknown” class at baseline.

In the analysis of medication use for the entire study duration (including baseline), more patients on Extraneal used medications in the most commonly used therapeutic classes, except for the classification of “unknown”. Summaries of concomitant medications by therapeutic class in which incidence of use differed by at least 5% between treatment groups in the Key Studies are presented in **Table 6F** (baseline data) and **Table 6G** (data during all study periods, including baseline).

Table 6F: Summary of Use of Concomitant Medications With ≥5% Difference Between Treatment Groups at Baseline – Key Studies

	Control Group (N=319)		Extraneal Group (N=391)	
Medication Therapeutic Class	**n**	**%**	**n**	**%**
Antithrombotic agents	68	21.3	120	30.7
Antacids, drugs for treatment of peptic ulcer and flatulence	70	21.9	109	27.9
Unknown	103	32.3	105	26.9
Beta blocking agents	44	13.8	85	21.7
Agents acting on the renin-angiotensin system	24	7.5	57	14.6
Cardiac therapy	25	7.8	52	13.3

Table 6G: Summary of Use of Concomitant Medications for All Study Periods With ≥5% Difference Between Treatment Groups – Key Studies

	Control Group (N=319)		Extraneal Group (N=391)	
Medication Therapeutic Class	**n**	**%**	**n**	**%**
Vitamins	195	61.1	261	66.8
Mineral supplements	193	60.5	257	65.7
Laxatives	118	37.0	165	42.2
Antibacterials for systemic use	110	34.5	161	41.2
Antacids, drugs for treatment of peptic ulcer & flatulence	94	29.5	154	39.4
Antithrombotic agents	96	30.1	152	38.9
Antihypertensives	81	25.4	127	32.5
Beta blocking agents	63	19.7	109	27.9
Unknown Class	103	32.3	106	27.1
Psycholeptics	65	20.4	100	25.6
Agents acting on the renin-angiotensin system	39	12.2	87	22.3
Cardiac therapy	34	10.7	72	18.4
Corticosteroids, dermatological preparations	14	4.4	38	9.7

6.1.2 Patient Disposition

Patient Disposition was evaluated for the integrated database of all studies as well as for Key and Supportive studies independently. Results for patient disposition were similar for Extraneal and Control groups (**Table 6H**).

In all clinical studies, approximately 66 % of Extraneal patients and 71% of control patients completed the study. Adverse experience was the most frequent reason for premature withdrawal in both groups (13.4% Extraneal, 11.8% Control), followed by Other (9.7% Extraneal, 6.9% Control), Transplantation (6.5% Extraneal, 4.6% Control), death and protocol violation. The category of “Other” includes patients who switched treatment modality (e.g. CAPD to APD), switched to hemodialysis, requested withdrawal for non-medical reasons, or regained renal function.

Table 6H: Disposition of Patients

	Control Group		Extraneal Group	
	n	%	n	%
ALL STUDIES	N=347		N=493	
Completed Study	246	70.9	323	65.5
Prematurely Discontinued Study	101	29.1	170	34.5
Transplantation	21	6.1	42	8.5
Adverse experience	41	11.8	66	13.4
Death	11	3.2	18	3.7
Protocol violation	11	3.2	7	1.4
Other	17	4.9	37	7.5

6.2 Adverse Events

6.2.1 Overall Adverse Events

An adverse event was defined as any untoward medical occurrence in a patient who had been enrolled in a study (baseline), which may or may not have a causal relationship with study treatment. Adverse events were recorded for the duration of the study as specified in the study protocol in all clinical trials. All patients who received at least one dose of study drug were included in the safety analyses.

A listing of all adverse events from the 840 patients in enrolled in the clinical studies for Extraneal, reported through the duration of the study, can be found in **Appendix 2**. At least one adverse event was reported by 87.0% of Extraneal and 84.1% of control patients. The extent of the adverse events reported was not unexpected due to the high number of comorbid conditions observed in end stage renal disease patient, regardless of the treatment modality for renal replacement therapy. The Healthcare Finance Administration (HCFA) medical evidence form describes hypertension (73.9%), diabetes (64.4%), congestive heart failure (33.4%) and ischemic heart disease (24.6%) as the most common comorbid conditions. The percentages of the patients in each treatment group having adverse events rated as severe and moderate were comparable.

Adverse events reported by ≥ 5% of patients in all studies, regardless of relationship assessment are presented in **Table 6I**. Only one event, rash, was identified as being reported with an incidence differing by 5% or more between treatment groups. Rash was reported by 10.1% of Extraneal patients as compared with 4.6% of Control patients.

Events reported with an incidence differing by 3% or more between treatment groups are shown below: hypotension and hypokalemia were reported by more patients in the Control group, while hypertension and rash were reported by more patients treated with Extraneal.

Rash	10.1% Extraneal,	4.6% Control
Hypertension	12.6% Extraneal,	8.4% Control
Hypotension	6.5% Extraneal,	10.7% Control
Hypokalemia	6.9% Extraneal,	10.7% Control

Overall, events described as possibly, probably, or definitely related to study drug were reported by 28.2% of Extraneal patients and 25.7% of control patients. Approximately one-third of patients with adverse events in either treatment group had no relationship assessments.

The percentages of reports of rash, hypertension, hypotension, and hypokalemia considered related to treatment for Extraneal and Control were:

Rash	5.5% Extraneal	1.7% Control
Hypertension	2.6% Extraneal	0.9% Control
Hypotension	3.2% Extraneal	4.9% Control
Hypokalemia	0% Extraneal	1.7% Control

The incidence of all adverse events reported as related (possibly, probably or definitely) is summarized in **Table 6J**.

Table 6I: Adverse Events Experienced by ≥5% of Patients by Body System and Preferred Term

COSTART BODY SYSTEM Preferred Term	Control Group (N=347)		Extraneal Group (N=493)	
	n	%	n	%
BODY GENERAL				
Peritonitis	88	25.4	130	26.4
Exit site infection	58	16.7	73	14.8
Pain	43	12.4	48	9.7
Headache	23	6.6	43	8.7
Pain, abdominal	20	5.8	39	7.9
Flu syndrome	21	6.1	35	7.1
Injury accidental	14	4.0	31	6.3
Asthenia	27	7.8	28	5.7
Lab test abnormality	12	3.5	25	5.1
Pain chest	12	3.5	25	5.1
Pain back	18	5.2	22	4.5
Infection	19	5.5	21	4.3
CARDIOVASCULAR				
Hypertension	29	8.4	62	12.6
Hypotension	37	10.7	32	6.5
DIGESTIVE				
Diarrhea	33	9.5	40	8.1
Nausea	17	4.9	35	7.1
Nausea vomiting	21	6.1	25	5.1
Dyspepsia	13	3.7	25	5.1
Vomiting	19	5.5	22	4.5
HEMATOLOGIC & LYMPHATIC				
Anemia	39	11.2	55	11.2
METABOLIC & NUTRITION				
Hypokalemia	37	10.7	34	6.9
Hypoproteinemia	32	9.2	34	6.9
Hypervolemia	20	5.8	28	5.7
Edema	17	4.9	28	5.7
Hyperphosphatemia	26	7.5	25	5.1
Hyperglycemia	12	3.5	25	5.1
Edema peripheral	29	8.4	18	3.7
MUSCULOSKELETAL				
Arthralgia	27	7.8	31	6.3
NERVOUS				
Dizziness	19	5.5	27	5.5
RESPIRATORY				
Upper respiratory infection	46	13.3	74	15.0
Cough increase	13	3.7	35	7.1
Dyspnea	24	6.9	26	5.3
SKIN				
Rash	16	4.6	50	10.1
Pruritus	23	6.6	27	5.5
Skin disease	18	5.2	11	2.2

Table 6J: Incidence of Related Adverse Eventsby COSTART Body System and Preferred Term (Page 1 of 4)

COSTART Body System	COSTART Preferred Term	Control Group (N=347) N	Control Group (N=347) Percent	Extraneal Group (N=493) N	Extraneal Group (N=493) Percent
BODY GENERAL	LAB TEST ABNORMALITY	6	1.7	13	2.6
	PAIN, ABDOMINAL	0	0.0	8	1.6
	HEADACHE	1	0.3	7	1.4
	ASTHENIA	4	1.2	6	1.2
	PERITONITIS	4	1.2	3	0.6
	FLU SYNDROME	0	0.0	3	0.6
	PAIN CHEST	1	0.3	2	0.4
	PAIN NECK	1	0.3	2	0.4
	PAIN	2	0.6	1	0.2
	PD CATH DYSFUNCTION	2	0.6	1	0.2
	EDEMA FACE	0	0.0	1	0.2
	EFFLUENT BLOODY	0	0.0	1	0.2
	INFECTION	0	0.0	1	0.2
	INJURY ACCIDENTAL	0	0.0	1	0.2
	PAIN BACK	2	0.6	0	0.0
CARDIOVASCULAR	HYPOTENSION	17	4.9	16	3.2
	HYPERTENSION	3	0.9	13	2.6
	HYPOTENS POST	2	0.6	1	0.2
	TACHYCARDIA	1	0.3	1	0.2
	CARDIOVASC DISEASE	0	0.0	1	0.2
	SYNCOPE	2	0.6	0	0.0
	CEREBROVASC ACCIDENT	1	0.3	0	0.0
	PALPITATION	1	0.3	0	0.0
DIGESTIVE	ANOREXIA	5	1.4	4	0.8
	DIARRHEA	0	0.0	3	0.6

Only one event per patient per preferred term was counted.
Events are ordered within each Body System from highest to lowest incidence rates within the Extraneal group.

Table 6J (Page 2 of 4) :Incidence of Related Adverse Events by COSTART Body System and Preferred Term

COSTART Body System	COSTART Preferred Term	Control Group (N=347)		Extrnael Group (N=493)	
		N	Percent	N	Percent
DIGESTIVE (CONT.)	LIVER FUNC ABNORM	0	0.0	3	0.6
	DYSPEPSIA	3	0.9	2	0.4
	NAUSEA VOMIT	1	0.3	2	0.4
	CONSTIP	0	0.0	2	0.4
	GI DIS	0	0.0	2	0.4
	NAUSEA	4	1.2	1	0.2
	VOMIT	1	0.3	1	0.2
	FLATUL	0	0.0	1	0.2
	GASTRITIS	0	0.0	1	0.2
	OBSTRUCT INTEST	0	0.0	1	0.2
	ULCER STOMACH	0	0.0	1	0.2
	GASTROENTERITIS	1	0.3	0	0.0
	STOOL ABNORM	1	0.3	0	0.0
HEMATOLOGIC AND LYMPHATIC	LEUKOCYTOSIS	0	0.0	3	0.6
	ANEMIA	0	0.0	2	0.4
	EOSINOPHILIA	2	0.6	1	0.2
METABOLIC AND NUTRITION	DEHYDRAT	5	1.4	10	2.0
	EDEMA PERIPH	4	1.2	7	1.4
	HYPOVOLEM	3	0.9	5	1.0
	HYPERVOLEM	5	1.4	4	0.8
	HYPOCHLOREM	0	0.0	4	0.8
	EDEMA	4	1.2	3	0.6
	WEIGHT INC	3	0.9	3	0.6
	PHOSPHATASE ALK INC	1	0.3	3	0.6
	HYPOPROTEINEM	4	1.2	2	0.4

Only one event per patient per preferred term was counted.
Events are ordered within each Body System from highest to lowest incidence rates within the Extraneal group.

Table 6J (Page 3 of 4) : Incidence of Related Adverse Events by COSTART Body System and Preferred Term

COSTART Body System	COSTART Preferred Term	Control Group (N=347)		Extraneal Group (N=493)	
		N	Percent	N	Percent
METABOLIC AND NUTRITION (CONT.)	HYPONATREM	3	0.9	2	0.4
	HYPOGLYCEM	2	0.6	2	0.4
	HYPOMAGNESEM	0	0.0	2	0.4
	SGOT INC	0	0.0	2	0.4
	SGPT INC	0	0.0	2	0.4
	HYPERGLYCEM	2	0.6	1	0.2
	WEIGHT DEC	0	0.0	1	0.2
	HYPOKALEM	6	1.7	0	0.0
	ULTRAFIL DEC	2	0.6	0	0.0
	CREATININE INC	1	0.3	0	0.0
MUSCULOSKELETAL	CRAMPS LEG	2	0.6	2	0.4
	MYALGIA	0	0.0	2	0.4
	CRAMPING	1	0.3	1	0.2
	PAIN BONE	0	0.0	1	0.2
NERVOUS	DIZZINESS	5	1.4	9	1.8
	PARESTHESIA	0	0.0	3	0.6
	DRY MOUTH	2	0.6	2	0.4
	ANXIETY	0	0.0	1	0.2
	HYPERKINESIA	0	0.0	1	0.2
	NERVOUSNESS	0	0.0	1	0.2
	THINKING ABNORM	0	0.0	1	0.2
	INSOMNIA	3	0.9	0	0.0
	SOMNOLENCE	3	0.9	0	0.0
	DEPRESSION	1	0.3	0	0.0
RESPIRATORY	DYSPNEA	1	0.3	2	0.4

Only one event per patient per preferred term was counted.
Events are ordered within each Body System from highest to lowest incidence rates within the Extraneal group.

Table 6J: (Page 4 of 4): Incidence of Related Adverse Events by COSTART Body System and Preferred Term

COSTART Body System	COSTART Preferred Term	Control Group (N=347)		Extraneal Group (N=493)	
		N	Percent	N	Percent
RESPIRATORY (CONT.)	LUNG DIS	0	0.0	2	0.4
	COUGH INC	0	0.0	1	0.2
	EDEMA LUNG	0	0.0	1	0.2
	HICCUP	0	0.0	1	0.2
	RHINITIS	1	0.3	0	0.0
	UPPER RES INFECT	1	0.3	0	0.0
SKIN	RASH	6	1.7	27	5.5
	DERM EXFOL	0	0.0	8	1.6
	PRURITUS	5	1.4	7	1.4
	NAIL DIS	0	0.0	3	0.6
	PSORIASIS	0	0.0	2	0.4
	RASH MAC PAP	3	0.9	1	0.2
	SKIN DIS	2	0.6	1	0.2
	ECZEMA	0	0.0	1	0.2
	FURUNCULOSIS	0	0.0	1	0.2
	RASH VESIC BULL	0	0.0	1	0.2
	SKIN DISCOLOR	0	0.0	1	0.2
	SKIN DRY	0	0.0	1	0.2
	ULCER SKIN	0	0.0	1	0.2
	URTICARIA	0	0.0	1	0.2
SPECIAL SENSES	TASTE LOSS	0	0.0	1	0.2
	TASTE PERVERS	1	0.3	0	0.0
UROGENITAL	PAIN KIDNEY	0	0.0	2	0.4
	EDEMA SCROTUM	1	0.3	0	0.0

Only one event per patient per preferred term was counted.
Events are ordered within each Body System from highest to lowest incidence rates within the Extraneal group.

6.2.2 Specific Adverse Events

6.2.2.1 Skin Adverse Events

Three specific events in the Skin body system were reported by at least 5% of the patients in either treatment group: rash (4.6% control, 10.1% Extraneal), pruritus (6.6% control, 5.5% Extraneal,), and skin disorder (5.2% control, 2.2% Extraneal).

Relationship of Skin Events to Study Treatment

Of Extraneal-treated patients reporting rash (52 patients, 10.5%), nineteen (3.9%) were considered unrelated, and 27 (5.5%) were assessed as related to treatment. In the Control patients reporting rash, 6 (1.7%) were considered related and 8 (2.3%) described as not related to treatment. Eight of 9 Extraneal-treated patients reporting exfoliative dermatitis (1.6%) had events considered related to study drug. The one report of exfoliative dermatitis in a control patient was assessed as not related to study treatment.

Of the 27 Extraneal patients (5.5%) reporting pruritus, 7 (1.4%) were assessed as related and 11 (2.2%) as not related. In the Control patients reporting pruritus, the relationships were 5 (1.4%) related and 9 (2.6%) not related.

Table 6K presents a summary of the relationship to study drug of the most commonly reported skin adverse events.

Table 6K: Incidence of Selected Skin Adverse Events by Relationship to Study Drug – All Studies

	Control Group (N=347)						Extraneal Group (N=493)					
COSTART	Not Related		Related		Not Recorded		Not Related		Related		Not Recorded	
Preferred Term	n	%	n	%	n	%	n	%	n	%	n	%
Dermatitis exfol	1	0.3	0	0	0	0	1	0.2	8	1.6	0	0
Eczema	1	0.3	0	0	0	0	1	0.2	1	0.2	4	0.8
Furunculosis	3	0.9	0	0	1	0.3	3	0.6	1	0.2	1	0.2
Herpes zoster	6	1.7	0	0	3	0.9	1	0.2	0	0	1	0.2
Nail dis	2	0.6	0	0	0	0	2	0.4	3	0.6	0	0
Pruritus	9	2.6	5	1.4	10*	2.9*	11	2.2	7	1.4	9	1.8
Rash	8	2.3	6	1.7	2	0.6	19	3.9	27	5.5	6	1.2
Rash vesic bull	8	2.3	0	0	1	0.3	2	0.4	1	0.2	3	0.6
Skin dis	14	4.0	2	0.6	2	0.6	9	1.8	1	0.2	2	0.4
Skin dry	3	0.9	0	0	0	0	6	1.2	1	0.2	3	0.6
Ulcer skin	11	3.2	0	0	2	0.6	15	3.0	1	0.2	1	0.2

*Values for pruritus include 1 control patient with preferred term of "pruritis."

Skin Serious Adverse Events and Skin Adverse Events Leading to Discontinuation

Thirteen patients, identified in **Table 6L**, all treated with Extraneal, were discontinued from the study due to an adverse event in the Skin system; one patient had two skin events (patient 37301 in Study RD-97-CA-131, with rash and dermatitis exfoliative). All but three of these events (2 events of ulcer skin and one event of pruritus) were considered related to study drug. All events except for the unrelated skin ulcer and the two events of pruritus (one unrelated and one possibly related) started within the first three weeks of study treatment.

Table 6L: Skin Adverse Events Leading to Discontinuation

Study	Patient ID	Preferred Term	Study Day at Onset of AE	Relationship to Study Drug	Severity Assessment
RD-97-CA-131	37301	Derm exfol	19	Definite	Mild
RD-97-CA-131	2401	Pruritus	52	None	Mild
RD-97-CA-131	17201	Pruritus	51	Possible	Severe
RD-97-CA-130	22101	Rash	1	Probable	Mild
RD-97-CA-130	33106	Rash	6	Probable	Moderate
RD-97-CA-131	19503	Rash	7	Possible	Severe
RD-97-CA-131	24401	Rash	5	Probable	Severe
RD-97-CA-131	37301	Rash	5	Definite	Moderate
RD-97-CA-131	45401	Rash	9	Probable	Moderate
RD-97-CA-131	33305	Rash vesic bull	21	Possible	Moderate
RD-97-CA-130	23208	Skin discolor	8	Probable	Mild
MIDAS-2	303	Ulcer skin	1210	None	Severe
MIDAS-2	307	Ulcer skin	1334	None	Moderate
RD-97-CA-130	23210	Urticaria	9	Probable	Severe

Exfoliative Dermatitis

Exfoliative dermatitis, was reported by one patient (0.3%) in the Control group, and by 9 patients (1.8%) in the Extraneal group. The term exfoliative dermatitis was determined by COSTART CODE to capture those skin events that were described by investigators as associated with peeling of the skin. This event was often preceded by a description of a skin event that used the term “rash”. None of the patients were evaluated by a dermatologist and the COSTART CODE was determined from the description of the skin event provided from the nephrologist investigator. Of the Extraneal patients reported to have exfoliative dermatitis, six continued in the study with resolution while on treatment, and one discontinued from the study.

There were no reports of anaphylaxis, Stevens-Johnson syndrome or other serious immune-mediated reactions associated with skin rash.

Conclusions on Skin Adverse Events

The incidence of skin rash in Extraneal treated patients appears to be approximately 5 percentage points higher than in patients treated with dextrose solutions. Six of the 14 patients who discontinued because of a skin disorder did so because of rash.

It is unclear whether the events reported as exfoliative dermatitis were true incidences or the result of COSTART coding of peeling associated with Rash. There were no manifestations of severe immune dysfunction such as Stevens-Johnson Syndrome, or anaphylaxis associated with reports of exfoliative dermatitis.

Skin rash is reported in post-marketing surveillance at no greater frequency than was observed in clinical trials. In general, in both clinical trials and post-marketing surveillance, the skin rash is usually mild to moderate and self-limited. It arises usually within one or two weeks of commencing therapy and resolves while on treatment in some patients and shortly after discontinuation in patients withdrawn from Extraneal treatment.

6.2.2.2 Peritonitis

In both treatment groups, peritonitis and exit site infection were the most common adverse events after 180 days and 360 days of treatment. The rates of peritonitis are similar between groups (25.8 months/episode for the Extraneal group, 24.4 months/episode for the active control group).

6.2.3 Serious Adverse Events

One or more serious adverse events were reported by 227 (31.5%) patients. The proportion of patients in each treatment group with serious adverse events was similar (31.7% Extraneal, 31.2% Control). Serious adverse events were reported by 143 patients (57, 51.4% Control and 86, 51.2% Icodextrin, p=1.000). Peritonitis was the most frequently reported SAE (5.3% Extraneal, 8.6% control). Serious adverse events reported by ≥0.5% of patients in either treatment group are presented in **Appendix 2**.

6.2.3.1 Mortality

Mortality analysis was originally planned for the 12 month safety study, RD-97-CA-131, following consultation with the Division of Cardio-Renal Drug Products (DCRDP) during protocol development. The protocol called for comparing mortality rates between Extraneal and the active control. Mortality was assumed to occur at a Poisson rate over time and equivalence would be established by constructing the 90% confidence interval around the difference between the estimated Poisson means.

The protocol defined data collection period for mortality data was for the duration of study participation (up to 12 months treatment) and for 30 days following study completion or termination. No statistically significant differences were observed when comparing the mortality rates for the two treatment groups (Extraneal vs. 2.5% Dextrose), although a numerical difference in the number of deaths and percentages of deaths between Extraneal and the Active Control was present.

Mortality in Controlled Clinical Studies

A review of all controlled clinical studies of Extraneal revealed several studies in which numerical differences in the numbers and percentages of deaths existed between the treatment groups. Two of these studies showed numerically greater numbers of deaths in the control group, two in the icodextrin group, and three studies showed no numerical difference. These data are illustrated in **Table 6M** below, and include all deaths reported, regardless of relationship to time of study participation or follow-up.

Table 6M: Deaths in Controlled Clinical Studies

Study	Design	Control			Extraneal		
		N	Deaths		N	Deaths	
			#	%		#	%
ML/IB/020 (DELIA)	Open-label crossover study for APD; 6 weeks duration	9	**0**	**0**	10	**0**	**0**
ML/IB/011 (DIANA)	Randomized open-label for CAPD; 24 months duration	19	**6**	**31.6**	19	**0**	**0**
ML/IB/001 (MIDAS)	Randomized open-label for CAPD; 6 months duration	103	**2**	**1.9**	106	**1**	**1.7**
PRO-RENAL-REG-035	Randomized open-label for APD; 16 weeks duration	19	**0**	**0**	20	**3**	**15**
RD-97-CA-130	Randomized blinded efficacy study; 4 weeks duration	23	**0**	**0**	23	**0**	**0**
RD-97-CA-131	Randomized blinded safety study; 52 weeks duration	112	**12**	**10.7**	175	**22**	**12.6**
RD-99-CA-060	Single dose pharmacokinetics study; 28 days duration	0	**0**	**0**	13	**0**	**0**
Total		285	**20**	**7.0**	366	**26**	**7.1**

In consult with the DCRDP, mortality analyses, as planned for the RD-97-CA-131 protocol, were performed for the combined data from all controlled studies of Extraneal. No difference in survival or causes of death were observed between Extraneal and Active Control (1.5%, 2.5% or 4.25% Dextrose) patients.

A Kaplan-Meier survival analysis for time to death was used with a logrank test to compare the groups and a Poisson model was assumed for the deaths so that the death rates per year were estimated for each group. **Table 6N** shows a total of 46 deaths (20 Control and 26 Extraneal) out of 651 patients (285 Control and 366 Extraneal). There were no statistically significant differences in survival (time to death) between the two groups (p=0.929).

Table 6N: Table of Mortality from All Controlled Studies Mortality Analysis Including Additional Follow-up Data Based on Survival Times in Days -- Survivors Have Censored Times

Group	No. Patients	No. Deaths	% Died	Quartiles for Survival (Days) 25th %	Median	75th %	Mean Times to Death and 90% Confidence Intervals (Days) Mean	Std Err	Lower	Upper	p-Value*
Control	285	20	7.0	481	558	N/A	508.0 #	12.62	487.3	528.8	0.929
Extraneal	366	26	7.1	704	N/A	N/A	636.3 #	17.68	607.2	665.4	
TOTALS	651	46	7.1	541	N/A	N/A	602.6 #	17.66	573.5	631.6	

* p-Value is from the LogRank test comparing the survival curves between groups.
# The mean and standard error were underestimated because the largest observation was censored.
N/A: there were not enough deaths to estimate this quartile.

Mortality Rates (per month and per year) based on Poisson Estimation showed a mean death rate per month of 0.009 for the Active Control group and 0.009 for the Extraneal group. The mean death rate per year was 0.11 (i.e., 11 deaths per 100 patient-years) for the Active Control group and 0.11 (i.e., 11 deaths per 100 patient-years) for the Extraneal group.

Table 6O: Mortality Rates (per Month and per Year) Based on Poisson Estimation

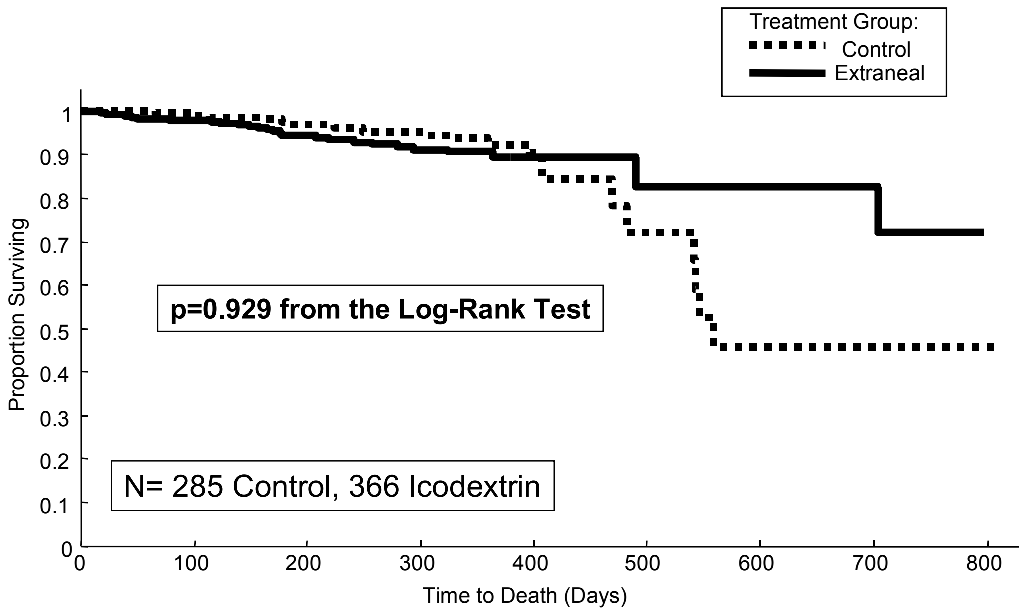
Treatment Group	No. Patients	Total Months	No. Deaths	Rates per Month@ Mean	Lower 90%	Upper 90%	Rates per Year@ Mean	Lower 90%	Upper 90%
Control	285	2268.7	20	0.009	0.000	0.163	0.11	0.00	1.96
Extraneal	366	2926.7	26	0.009	0.000	0.164	0.11	0.00	1.97

@ the estimated mean and 90% confidence interval are displayed.

Table 6P: Differences Between Mortality Rates (per Month and per Year)
Based on Poisson Equivalence of Extraneal and Control Based on Ninety Percent (90%) Confidence Intervals

Icodextrin Mean	Control Mean	Difference (Ext - Cntl)	Std Error of Difference	Equivalence Based on Deaths per Month Lower 90%	Upper 90%	Equivalence Based on Deaths per Year (Ext - Cntl)	Lower 90%	Upper 90%
0.009	0.009	0.000	0.0026	-0.004	0.004	0.001	-0.051	0.053

Figure 6A: Kaplan Meier Survival Curves for All Controlled Clinical Studies.



Mortality in RD-97-CA-131,13 Month Follow-up

The original protocol required follow-up of one month following completion of the 12-month study, or from the time of study termination. The protocol was amended, based upon input from the October 2000 Closed Cardio-Renal Advisory Committee Meeting, to include 13-month follow-up for purposes of mortality.

A retrospective follow-up of patients who prematurely discontinued from the study and did not have an outcome of "death" was performed. Study sites were questioned regarding the status, 13 months after study initiation, for those patients who had prematurely discontinued from the study and were not identified as deceased one month after termination. There were a total of 101 patients who fit this criterion. The status of the patient was to be recorded as "living," "unknown" or "deceased." Data for 98 of 101 eligible patients was obtained. Three patients were determined lost to follow-up.

A Kaplan-Meier survival analysis for time to death was used with a logrank test to compare the groups and a Poisson model was assumed for the deaths so that the death rates per year were estimated for each group. **Table 6Q** shows a total of 29 deaths (9 Control and 20 Extraneal) out of 287 patients (112 Control and 175 Extraneal) and **Table 6R** provides the causes of death.

Table 6Q: Mortality Analysis Including Additional Follow-up Data
Based on Survival Times in Days -- Survivors Have Censored Times

Group	No. Patients	No. Deaths	% Died	Quartiles for Survival (Days) 25th %	Median	75th %	Mean Times to Death and 90% Confidence Intervals (Days) Mean	Std Err	Lower	Upper	p-Value*
Control	112	9	8.0	N/A	N/A	N/A	384.8 #	4.40	377.6	392.1	0.301
Extraneal	175	20	11.4	N/A	N/A	N/A	343.9 #	5.07	335.5	352.2	
TOTALS	287	29	10.1	N/A	N/A	N/A	376.6 #	3.86	370.2	382.9	

* p-Value is from the LogRank test comparing the survival curves between groups.
\# The mean and standard error were underestimated because the largest observation was censored.
N/A: there were not enough deaths to estimate this quartile.

Table 6R: Causes of Death

Causes of Death	Control N (%)	Extraneal N (%)
Cardiac Arrest or Myocardial Infarction	4 (44%)	11 (55%)
Pneumonia	2 (22%)	0 (0%)
Unknown	2 (22%)	1 (5%)
Renal Failure/ESRD	0 (0%)	2 (10%)
CVA	0 (0%)	2 (10%)
Sepsis	0 (0%)	1 (5%)
Peripheral Vascular Disease/ESRD	0 (0%)	1 (5%)
Bowel Infarction, post MI	0 (0%)	1 (5%)
Withdrawal from Dialysis	0 (0%)	1 (5%)
Multi-System Organ Failure	1 (11%)	0 (0%)

There were no statistically significant differences in survival (time to death) between the two groups (p=0.301).

Mortality Rates (per month and per year) based on Poisson Estimation show a mean death rate per month of 0.007 for the control group and 0.010 for the Extraneal group. The mean death rate per year was 0.08 (i.e., 8 deaths per 100 patient-years) for the Control group and 0.12 (i.e., 12 deaths per 100 patient-years) for the Extraneal group.

Table 6S: Mortality Rates (per Month and per Year)
Based on Poisson Estimation

Group	No. Patients	Total Months	No. Deaths	Rates per Month@ Mean	Lower 90%	Upper 90%	Rates per Year@ Mean	Lower 90%	Upper 90%
Control	112	1356.1	9	0.007	0.000	0.141	0.08	0.00	1.69
Extraneal	175	2009.6	20	0.010	0.000	0.174	0.12	0.00	2.09

@ the estimated mean and 90% confidence interval are displayed.

Table 6T demonstrates the equivalence of the Extraneal and Control groups based on 90% confidence intervals.

**Table 6T: Differences Between Mortality Rates (per Month and per Year)
Based on Poisson Estimation: Equivalence of Extraneal and Control Based on Ninety Percent (90%) Confidence Intervals**

Icodextrin	Control	Difference	Std Error of	Equivalence Based on Deaths per Month		Equivalence Based on Deaths per Year		
Mean	Mean	(Ext - Cntl)	Difference	Lower 90%	Upper 90%	(Ext - Cntl)	Lower 90%	Upper 90%
0.010	0.007	0.003	0.0031	-0.002	0.008	0.040	-0.022	0.102

Mortality Analysis of RD-97-CA-131, All known Deaths

During the collection of 13-month follow-up data, some of the clinical sites provided information for patients beyond the 13 months following study termination. This resulted in identification of five patients (3 control, 2 icodextrin) who had died beyond 13 months following study initiation. These patients were included in the all controlled studies analysis presented in Section 6.3.4.1. Mortality analysis for all known deaths from RD-97-CA-131 are presented below demonstrated no differences in the survival times or mortality rates for Extraneal or Control patients. The results of these analyses are presented in Tables 6U, 6V and 6W.

**Table 6U: Table of All Mortality from Study RD-97-CA-131
Mortality Analysis Including All Additional Follow-up Data
Based on Survival Times in Days -- Survivors Have Censored Times**

Group	No. Patients	No. Deaths	% Died	Quartiles for Survival (Days)			Mean Times to Death and 90% Confidence Intervals (Days)				p-Value*
				25th %	Median	75th %	Mean	Std Err	Lower	Upper	
Control	112	12	10.7	407	469	558	459.9	34.43	403.3	516.6	0.610
Extraneal	175	22	12.6	490	490	704	549.5	69.15	435.8	663.3	
TOTALS	287	34	11.8	469	490	558	502.7	40.09	436.8	568.7	

No.= number
* p-Value is from the LogRank test comparing the survival curves between groups.
\# The mean and standard error were underestimated because the largest observation was censored.
N/A: there were not enough deaths to estimate this quartile.

Table 6V: Mortality Rates (per Month and per Year)
Based on Poisson Estimation

Treatment Group	N0. Patients	Total Months	No. Deaths	Rates per Month@			Rates per Year@		
				Mean	Lower 90%	Upper 90%	Mean	Lower 90%	Upper 90%
Control	112	1364.2	12	0.009	0.000	0.163	0.11	0.00	1.96
Extraneal	175	2022.9	22	0.011	0.000	0.182	0.13	0.00	2.19

No.= number
@ the estimated mean and 90% confidence interval are displayed.

Table 6W: Differences Between Mortality Rates (per Month and per Year) Based on Poisson Estimation
Equivalence of Icodextrin and Control Based on Ninety Percent (90%) Confidence Intervals

Icodextrin Mean	Control Mean	Difference (Ext - Cntl)	Std Error of Difference	Equivalence Based on Deaths per Month		Equivalence Based on Deaths per Year		
				Lower 90%	Upper 90%	(Ext - Cntl)	Lower 90%	Upper 90%
0.011	0.009	0.002	0.0034	-0.004	0.008	0.025	-0.043	0.093

EXT = Extraneal
Cntl = Control

Mortality Conclusions

No statistically significant difference in mortality rates or survival were observed for either the RD-97-CA-131 original protocol, 13-month amended protocol, or all controlled studies analyses.

Review of narratives for patient deaths indicated that causes of death were not different in the active control and icodextrin patients. Although statistically the numbers of patient deaths were too small to permit appropriate subgroup analyses, exploratory analyses were conducted and failed to reveal any biologically or clinically meaningful co-variates to therapy, which increased the risk of mortality.

As none of the studies were adequately powered to demonstrate a statistical difference in mortality, and in light of the small number of deaths, even when controlled study data is combined, results of these studies should be considered observational.

6.3 Clinical Laboratory Evaluations

Unless otherwise noted, discussions of laboratory results are for the All Studies population. Reference ranges were obtained for ESRD patients; for analytes not included in that table, standard reference normal ranges were used. Incidences of laboratory values reported as AEs are discussed in this section only for selected analytes; a complete presentation of laboratory AEs (by COSTART body system and preferred term) may be found in **Appendix 2.**

6.3.1 Sodium

Mean values for sodium were within normal limits at each time point for both treatment groups, but the mean values for Extraneal were consistently near the lower limit of normal (normal range 135 - 148 mmol/L; range of mean values for Extraneal patients 135.3 – 135.7 mmol/L) (**Table 6X**). While there were downward trends in mean changes from baseline in both treatment groups, the changes ranged from -0.58 to +0.038 mmol/L in the active control group and from -3.59 to -2.74 mmol/L in the Extraneal group. Differences in mean changes between treatment groups were statistically significant at each time point measured ($p < 0.001$). Minimum values were comparable between treatment groups at each time point including baseline, ranging from 124 – 128 mmol/L in the active control group and from 119 – 126 mmol/L in the Extraneal group.

Table 6X: Mean Values and Mean Changes From Baseline in Sodium (mmol/L) – All Studies

Visit	Treatment Group	N	Data Mean	Data SE	Change From Baseline Mean	Change From Baseline SE
Baseline	Control	341	138.431	0.195	--	--
	Extraneal	472	138.530	0.160	--	--
One Month	Control	269	138.141	0.241	-0.242	0.209
	Extraneal	299	135.592	0.212	-2.744	0.217
3 Months	Control	217	138.180	0.234	-0.343	0.230
	Extraneal	265	135.694	0.211	-2.924	0.233
6 Months	Control	173	138.075	0.288	-0.578	0.320
	Extraneal	262	135.340	0.208	-3.597	0.224
1+ Year	Control	80	138.338	0.440	0.038	0.490
	Extraneal	157	135.752	0.245	-3.142	0.310
Last Visit	Control	329	138.161	0.214	-0.272	0.219
	Extraneal	451	135.796	0.156	-2.771	0.180

SE=standard error

The mean decreases from baseline in the Extraneal group are related to a dilutional effect caused by elevated blood levels of icodextrin metabolites, particularly maltose and maltotriose. The presence of osmotically active particles in the vascular compartment is sufficient to cause a slight shift in water from the cellular to the vascular compartment, resulting in the observed declines.[7]

Incidences of hyponatremia as an AE were comparable between treatment groups (2.0% control, 7 patients; 2.2% Extraneal, 11 patients) (**Appendix 2**). Three patients (0.9%) in the control group and 2 patients (0.4%) in the Extraneal group reported hyponatremia considered to be related to study drug. The majority of hyponatremic events were mild in severity; none was reported as severe. Based upon the clinical trial results, no clinical relevance could be attributed to the change in sodium in this patient population.

6.3.2 Chloride

Mean values for chloride were near the lower limit of normal (normal range 96 –112 mmol/L) for the active control group at all time points, and slightly below normal for the Extraneal group at all post-baseline time points (range 94.5 – 95.8 mmol/L) (**Table 6Y**).. Mean changes from baseline in the Extraneal arm ranged from -2.54 to -1.73 mmol/L, while mean changes from baseline in the control group were consistently minimal increases (range +0.485 to +0.764 mmol/L). Analysis of mean changes from baseline between treatment groups revealed statistically significant differences at all post-baseline time points between treatment groups ($p < 0.001$ at all time points except at 1+ year where $p = 0.005$).

As with the mean decreases in sodium, the mean decreases in chloride in the Extraneal group are due to the dilutional effects as explained above.

Table 6Y: Mean Values and Mean Changes From Baseline in Chloride (mmol/L) – All Studies

Visit	Treatment Group	N	Data Mean	Data SE	Change From Baseline Mean	Change From Baseline SE
Baseline	Control	268	96.795	0.301	--	--
	Extraneal	374	96.902	0.275	--	--
One Month	Control	216	97.319	0.344	0.633	0.244
	Extraneal	253	94.747	0.296	-1.729	0.282
3 Months	Control	177	98.264	0.402	0.485	0.306
	Extraneal	227	95.203	0.298	-2.325	0.301
6 Months	Control	142	98.761	0.448	0.567	0.399
	Extraneal	210	95.862	0.333	-2.538	0.349
1+ Year	Control	79	97.165	0.514	0.764	0.584
	Extraneal	136	94.566	0.631	-2.435	0.803
Last Visit	Control	285	97.627	0.306	0.610	0.263
	Extraneal	395	95.149	0.291	-2.003	0.348

SE=standard error

Hypochloremia was reported as an AE by 3 (0.9%) active control patients and 8 (1.6%) Extraneal patients; half of the Extraneal patients reported hypochloremia that was considered related to study drug. All reported events of hypochloremia were assessed as mild in severity except for one event assessed as moderate in the Extraneal group.

6.3.3 Serum Amylase

Mean values for serum amylase were markedly lower in the Extraneal group (range 17.3 – 29.1 U/L) compared with the control group (range 93.0 – 118.9 U/L) (**Table 6Z**). In the control group, mean changes from baseline ranged from -6.045 to -1.677 U/L (the higher mean values are due to outliers; the maximum values at the 1, 3, and 6 month time points were >1100 U/L). In the Extraneal group, mean changes from baseline were greater than -80 U/L at all time points, ranging from -108.426 to -81.004 U/L (representing a 73.5% to 86.2% decline). The differences between treatment groups in the mean changes from baseline were statistically significant at all time points (p <0.001 at each time point).

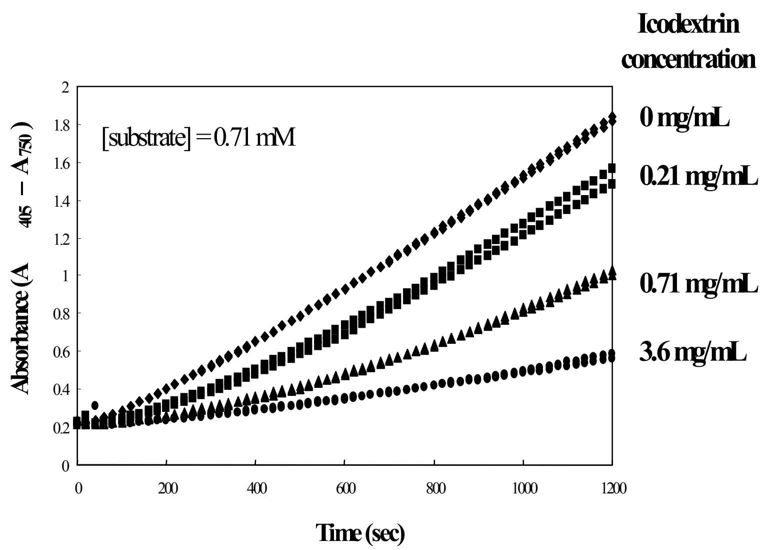
Table 6Z: Mean Values and Mean Changes From Baseline in Serum Amylase (U/L) – All Studies

Visit	Treatment Group	N	Data Mean	Data SE	Change From Baseline Mean (% drop)	Change From Baseline SE
Baseline	Control	216	96.444	3.577	--	--
	Extraneal	286	98.623	3.499	--	--
One Month	Control	169	107.527	8.508	-1.677 (1.7%)	1.780
	Extraneal	136	19.435	1.314	-95.198 (83.0%)	5.201
3 Months	Control	119	112.235	14.233	-4.414 (4.6%)	2.590
	Extraneal	131	29.053	2.590	-81.115 (73.6%)	5.630
6 Months	Control	89	118.921	16.947	-5.824 (6.0%)	3.625
	Extraneal	92	21.837	2.576	-95.304 (81.4%)	6.798
1+ Year	Control	66	92.985	6.063	-6.045 (6.3%)	4.042
	Extraneal	61	17.311	1.304	-108.426(86.2%)	7.639
Last Visit	Control	212	105.524	7.659	-3.784 (3.9%)	2.179
	Extraneal	221	27.517	1.972	-81.004 (74.6%)	4.343

SE=standard error

The decline in serum amylase activity is an artefact due to interference by icodextrin in the amylase activity assay. Icodextrin acts as a competitive inhibitor of the substrate used in standard clinical chemistry assays for amylase activity. The substrate, 4,6-ethylidene-G7-PNP, contains a linear chain of seven glucose units linked by alpha 1-4 glucosidic bonds resembling the structure of icodextrin. An example of the competitive inhibition due to icodextrin using a standard amylase assay kit and typical substrate concentration is shown in **Figure 6B**. Concentrations of icodextrin of 3.6 mg/mL (less than steady-state levels of icodextrin in patients treated with Extraneal) resulted in a significant (>70%) decrease in amylase activity. Additional external investigations confirm that icodextrin interferes in the measurement of amylase activity.[8] In conclusion, the observed decrease in serum amylase is an artefact due to competitive inhibition in the amylase activity assay.

Figure 6B: Kinetics of color formation in amylase activity assay in the presence of icodextrin.



6.3.4 Alkaline Phosphatase

Mean values for alkaline phosphatase were higher at all time points in the Extraneal group compared with the active control group, as were mean changes from baseline (Extraneal range 13.417 – 24.864 U/L; control range 1.096 – 6.769 U/L) (**Table 6AA**). However, mean values for alkaline phosphate were within normal limits for ESRD patients (31 – 115 U/L) at all time points and mean changes from baseline were also increased in the control arm at all but one time point (a mean decrease of -2.527 U/L at 1 month).

Table 6AA: Mean Values and Mean Changes From Baseline in Alkaline Phosphatase (U/L) – All Studies

	Treatment		Data		Change From Baseline	
Visit	**Group**	**N**	**Mean**	**SE**	**Mean**	**SE**
Baseline	Control	214	89.107	3.667	--	--
	Extraneal	294	92.476	3.315	--	--
One Month	Control	167	85.383	3.547	-2.527	1.292
	Extraneal	192	110.068	5.164	15.142	2.194
3 Months	Control	116	92.724	5.169	1.096	5.034
	Extraneal	165	98.533	3.778	13.417	1.953
6 Months	Control	85	100.600	6.244	6.607	6.171
	Extraneal	132	100.924	3.902	15.800	3.700
1+ Year	Control	66	102.818	7.043	6.769	7.068
	Extraneal	104	111.423	10.401	24.864	10.525
Last Visit	Control	208	93.625	3.745	4.039	2.885
	Extraneal	278	111.428	5.251	19.073	4.247

SE=standard error

In general, the increase in alkaline phosphatase associated with Extraneal, per se, was mild (average increase 17.3 U/L) and not associated with adverse events or abnormalities in other liver function tests. Alkaline phosphatase levels in most patients treated with Extraneal remained within the normal range. At baseline, 58 (19.7%) of Extraneal patients were above the normal range and 233(79.3%) were within the normal range. In the Control group at baseline, 33 (15.4%) of patients were above the normal range and 179 (83.7%) were within the normal range. During the study, 70(32%) shifted from normal to a high value in the Extraneal group and 35 (20.3%) of the Control patients shifted from normal to a high value. In general, there was an association between elevated alkaline phosphatase levels and elevated transaminase levels in the Control patients. However, this association was not present in the Extraneal patients with elevated alkaline phosphatase levels. This suggests that the elevation in alkaline phosphatase in the Extraneal group was less likely to be associated with other liver function test abnormalities, while in the Control group elevations in alkaline phosphatase were more likely to be associated with elevations in other liver function tests.

Adverse Events recorded as "alkaline phosphatase increase" occurred in 2.8% (n=14) of patients in the Extraneal group and 1.7% (n=6) of patients in the control group. All reported events of increased alkaline phosphatase were mild or moderate in intensity. Three patients in the

Extraneal group (0.6%) and one patient in the control group (0.3%) reported increased alkaline phosphatase considered related to study drug. The increases in alkaline phosphatase were not associated with clinical sequelae and remained level throughout the study. In the study where there was follow up data (PRO-RENAL-REG-035), alkaline phosphatase levels returned to baseline coincident with the return of icodextrin and metabolite blood levels to baseline. Therefore, the elevation in alkaline phosphatase was not considered to be indicative of a permanent or significant alteration in liver function.

In the long term study (RD-CA-97-131), four patients who died were identified with increased alkaline phosphatase and increased transaminase levels. Of these patients, one had both increased alkaline phosphatase and transaminase concentrations at baseline, one had increased alkaline phosphatase at baseline and in this patient transaminase levels increased during the study. The remaining two patients had increased alkaline phosphatase and transaminase levels during the study, but the baseline values were normal. A review of the narratives of adverse events in these patients did not reveal any clinical condition that would explain the elevation in alkaline phosphatase or transaminase levels.

6.4 Edema, Weight Gain, Quality of Life

6.4.1 Edema

Evidence of fluid imbalance was evaluated by changes in weight and by signs/symptoms of edema. Body weight was collected at baseline and end of study (week 4) for study RD-97-CA-130 as part of the vital signs assessment. This was part of the physical examination and the site was asked to record whether the weight was taken before or after drain. In Study RD-97-CA-131, body weight was collected at baseline, weeks 13, 26, 39 and 52. As in study 130 the site was asked to record whether the weight was taken before or after drain. The sites were not given identical scales or instructions on type of clothing to be worn during the weigh data collection.

Edema was also measured at baseline and end of study (Week 4) for study RD-97-CA-130 as part of the vital signs assessment. The sites were asked to assess the patient's edema by rating any peripheral edema on a subjective scale of 0 to 4+. If the patient's edema status was 0 to 3+, the site was to check the appropriate rating box. If the patient's edema status was 4+ or greater, the site was to document this as an adverse event. In Study RD-97-CA-131, edema was collected at baseline, weeks 13, 26, 39 and 52. As in study 130, edema was documented in the same manner.

A significant difference was observed between the two treatment groups in the number of patients with no edema at Weeks 26 and 39 in the RD-97-CA-131 study. At both time periods (Weeks 26 and 39), approximately 65% of the Control patients had no edema compared to approximately 80% of the Extraneal patients. However, these differences were no longer evident at Week 52, when approximately 76% of all patients had no edema.

There was a significant difference (p=0.033) at Week 52 in patients who had a shift from no edema to some edema, or vice versa, within the Extraneal Group. This shift in edema was not observed for patients within the Control Group. Sixteen of 89 Extraneal patients (18.0%) went from no edema to some edema and 6 of 14 (42.9%) Extraneal patients went from some edema at Baseline to no edema at the end of study. Similarly, 8 of 44 Control patients (18.2%) went from no edema at Baseline to some edema at the end of study and 10 of 18 Control patients (55.6%) went from some edema to no edema. There was also a higher incidence of adverse events for peripheral edema (defined as 4+ edema) in the active control group compared to the Extraneal group (17.9% vs. 6.3%).

The lower incidence of peripheral edema in the Extraneal group coupled with the demonstrable increase in net ultrafiltration supports the use of Extraneal in the long dwell to help manage fluid balance in patients on peritoneal dialysis.

6.4.2 Weight Gain

Although information on body weight was collected as part of physical examination data in most Key and Supportive Studies, only Studies RD-97-CA-130 and RD-97-CA-131 collected data that were specifically related to body weight either before or after drain. Therefore, only results from these two studies are being used in this discussion of short-term and long-term weight gain during the study. **Table 6BB** presents a summary of these data.

Table 6BB: Mean Changes in Body Weight Before Drain (kg)

	Control Group	Extraneal Group	P Between
Study RD-97-CA-130			
Week 2			
N	66	65	
Mean Change from Baseline	0.64	-0.17	0.019
Week 4			
N	66	64	
Mean Change from Baseline	0.80	0.79	0.943
Study RD-97-CA-131			
Week 2			
N	48	54	
Mean Change from Baseline	0.75	-0.35	0.009
Week 4			
N	49	56	
Mean Change from Baseline	1.05	0.60	0.425
Week 13			
N	76	116	
Mean Change from Baseline	0.83	-0.51	0.005
Week 26			
N	65	111	
Mean Change from Baseline	0.44	-0.27	0.204
Week 39			
N	58	96	
Mean Change from Baseline	1.00	-0.06	0.182
Week 52			
N	47	88	
Mean Change from Baseline	2.33	-0.03	0.022

SE= standard error, p Between = p value from analysis of covariance for significant differences across treatment groups for mean changes from baseline.

In Study RD-97-CA-130, measurements of body weight before drain were recorded as part of the physical examination data at baseline and at Weeks 2 and 4. A statistically significant difference between the two treatment groups in mean body weight before drain was noted at baseline (control 74.2 kg, Extraneal 79.6 kg; p= 0.044). During the study, there were statistically significant differences within treatment groups for body weight before drain at several time points. The control group experienced mean increases in body weight at Weeks 2 and 4 (0.64 kg, p = 0.005 at Week 2 and 0.80 kg, p = 0.008 at Week 4), while the Extraneal group experienced a mean decrease in body weight at Week 2 (-0.17 kg, p = 0.474) and a mean increase in body weight at Week 4 (0.79, p = 0.022). At Week 2, the difference between treatment groups in mean body weight was statistically significant (p = 0.019). These short-term changes in body weight are most likely related to fluctuations in fluid balance.

In Study RD-97-CA-131, body weight before or after drain was recorded at baseline and at Weeks 2, 4, 13, 26, 39, and 52. Each patient was weighed either before or after the drain; no patient was weighed at both times. A larger number of patients were weighed before drain than after drain. Only those patients who rolled over from Study RD-97-CA-130 had body weight measurements at Weeks 2 and 4 (these measurements were carried forward from that study). No statistically significant difference was noted between treatment groups in body weight at baseline. At each follow-up visit, there were trends for patients in the control group to gain weight and for patients in the Extraneal group to lose or maintain weight measured before drain. Patients in the control group had statistically significant weight increases before drain at Weeks 2, 4, 13, and 52. Additionally, there were statistically significant differences in body weight changes before drain between the two treatment groups at Week 2 (p = 0.009), Week 13 (p = 0.005), and Week 52 (p = 0.022). At Week 52, the control patients had gained an average of 2.33 kg while the Extraneal patients had lost an average of 0.03 kg in body weight before drain. For the small number of patients that were weighed after the drain, there was no difference in body weight between the two groups.

Dextrose-treated patients had a significant increase in body weight compared with Extraneal-treated patients. The short-term changes in body weight were most likely related to changes in fluid balance. The overall weight gain in the control patients over the course of the one-year study was most likely related to increased body fat due to the glucose load inherent in dextrose-based solutions.[9] The lack of weight gain in Extraneal patients may suggest a benefit of Extraneal in reducing weight gain due to excess glucose load in peritoneal dialysis patients.

There were no notable differences between the two treatment groups in reported AEs related to increased or decreased body weight.

6.4.3 Quality of Life

Evaluation of quality of life with the KDQol instrument was introduced as a study amendment and hence only a portion of the patients enrolled in the study were able to complete a baseline evaluation. Patients completed forms to assess symptoms/problems and overall quality of life during the 1-year study, RD-CA-97-131. The KDQoL Questionnaire contained a 35-item symptom/problem list and the Short Form-36, a 36-item questionnaire characterizing the patient's general health status. Patients indicated to what extent during the prior 30 days they were bothered by each of 35 symptoms. Each item was scored on a 5-point scale ("not at all," "somewhat," "moderately," "very much," or "extremely"). Raw scores for the 36 items were linearly transformed to 0 to 100 scales with 0 being the lowest value and 100 being the highest possible value. Higher transformed scores indicate better health.

For patients who completed both the Baseline and the Week 52 KDQoL forms (N=25 Control, N=41 Extraneal), the overall scores for the Symptom/Problem items did not change significantly from Baseline to Week 52 within either treatment group. Furthermore, at the item level, no statistical differences were detected when the mean changes in scores were compared between treatment groups.

There were some KDQoL Symptom/Problem items for which the differences in change from Baseline to Week 52 between treatment groups exceeded 5 points. A treatment group was defined to have an advantage when it possessed a treatment difference of at least 5 points when comparing score changes from Baseline to Week 52. If the absolute difference between groups was less than 5 points, it was determined that there was no advantage to either group. There was a meaningful difference favouring the Extraneal Group in 10 items while there was a clinically meaningful difference favoring the Control Group in 5 items. Neither group had an advantage in the other 20 items. **Table 6CC** displays this data. Most importantly, when asked to compare their health in general at week 52 versus baseline, as significantly greater percentage (30%) of patients in the Extraneal group stated they felt better, while only 4% of patients in the control group stated they felt better ($p<0.03$).

Table 6CC: KDQoL Symptom/Problem Items – Comparison Between Treatment Groups for Change from Baseline to Week 52 for Patients Who Completed Both Forms

Treatment Advantage* for Symptom/Problem Items	
Control Group	**Icodextrin Group**
e. Ache in bones	a. Soreness in your muscles
h. Headaches	d. Stiffening of joints
i. Cramps during an exchange or treatment	p. Faintness or dizziness
s. Dry mouth	r. Loss of taste
dd. Hot or cold spells	u. Lack of strength
	v. Fatigue, weakness
	w. Washed out or drained
	x. Numbness in hands or feet
	z. High blood pressure
	gg. Blurred vision

*Based on clinically meaningful differences between treatment groups. For this analysis, clinically meaningful is defined as a ≥5 point difference between groups when comparing the change in score from Baseline to Week 52. Using item (a) *Soreness in your muscles* for patients who completed both the Baseline and Week 52 KDQoL forms, the difference between the Icodextrin Group (+3.7) and the Control Group (-4.2) change in score is 7.9 points in favor of Icodextrin.

6.5 Other Safety Information

6.5.1 Post-marketing Safety Data

Extraneal has been approved in 28 countries worldwide, with a total market exposure of 187,081 patient months through January 31, 2001. Market exposure is calculated by dividing the total number of bags produced by 30, which is the number of bags an individual patient would use in one month. There were 5,612,438 bags produced in the period from March 1998 to Jan 31, 2001. It has also been used under compassionate use in with a patient exposure of 2,429 patient months.

From Feb. 1, 1997 to Jan 31, 2001, the most common adverse events reported in spontaneous notifications were events related to the skin (1.5%). The other notifications were those generally associated with peritoneal dialysis therapy, such as peritonitis or those related to underlying co-morbid conditions. None of the notifications were for events that had not been seen in clinical trials. Labeling changes have been made to the approved worldwide labeling to include a statement in the Precautions section concerning a rise in alkaline phosphatase levels seen in clinical trial results and an increased in frequency of skin rash due to information gained from Baxter sponsored clinical trial reports.

6.6 Safety Conclusions

Data from 493 Extraneal patients and 347 control patients presented show that Extraneal is safe and well tolerated as a peritoneal dialysis solution. Patients included in this summary had a mean exposure to Extraneal of almost 6 months (232.5 days) and a maximum exposure of more than 44 months (1326 days).

The overall adverse event profile for Extraneal-treated patients was generally similar to that of control patients in incidence rates and assessments of severity. Slightly more Extraneal patients had one or more adverse events considered possibly, probably, or definitely related to study drug (28.2% Extraneal, 25.7% control). There were no statistically significant differences in survival time between groups, and no deaths in either treatment group were considered related to study drug.

The only body system with notable differences in adverse events between treatment groups was Skin. Extraneal-treated patients had a 4.5% higher incidence of dermatological events compared with the control population. Rash was reported by 10.1% of Extraneal patients, compared with 4.6% of control patients, and exfoliative dermatitis was reported by 1 control and 9 Extraneal (1.8%) patients. Most Skin adverse events were mild or moderate in intensity; only 6 Skin events (5 Extraneal, 1 control) were reported as serious adverse events and none of these events was considered related to study drug. All 14 Skin events leading to discontinuation of study drug were reported by Extraneal-treated patients (one patient had two Skin events leading to discontinuation); 11 of 14 were considered related to study drug and 3 of these related events were severe in intensity.

Abnormalities were noted in Extraneal-treated patients in selected analytes (lowered sodium and chloride levels and alkaline phosphatase) but these changes were not clinically meaningful. Serum amylase levels in Extraneal patients were markedly lower than control patients due to interference from Extraneal with amylase activity for the assay.

Analyses of commonly reported adverse events occurring after 6 months and 12 months of Extraneal therapy were generally lower than the overall incidence of these adverse events; there appears to be no cumulative adverse effect of Extraneal.

In conclusion, Extraneal is a well-tolerated dialysate for the long dwell exchange in continuous ambulatory peritoneal dialysis (CAPD) or Automated Peritoneal Dialysis (APD).

7.0 BENEFIT/RISK SUMMARY

Currently marketed peritoneal dialysis solutions in the United States utilize glucose as the osmotic agent. The primary drawback of glucose as an osmotic agent is inadequate ultrafiltration during long dwell exchanges. Baxter Healthcare developed Extraneal primarily to provide the peritoneal dialysis patient with a more efficient alternative for the long dwell exchange to enhance ultrafiltration and therefore potentially extend the viability of this therapy.

7.1 Benefits

The efficacy of isosmotic Extraneal was compared with hyperosmotic dextrose solutions during single daily dwells of 8 to 16 hours in three key studies, ML/IB/001 (MIDAS), RD-97-CA-130, and PRO-RENAL-REG-035.

The pooled results from the three key studies these data demonstrate that Extraneal provides statistically greater net UF at all dwell times as compared with either 1.5% or 2.5% dextrose ($p<0.001$).

The increased net UF observed with Extraneal was associated with greater peritoneal clearance of creatinine and urea nitrogen or urea as well. The efficacy data from the 3 key studies also show that the number of patients who experienced negative net UF was significantly reduced in Extraneal-treated patients compared with dextrose-treated patients who received either 1.5% or 2.5% dextrose ($p<0.001$). In general, the net UF and peritoneal creatinine, urea nitrogen and urea clearance results of the subgroup analyses for age, gender, diabetes, hypertension, and race were similar to those of the main population.

In a fourth controlled study of Extraneal (Study RD-97-CA-131), dextrose-treated patients had statistically significant increases from baseline in body weight compared with Extraneal-treated patients ($p=0.022$ at week 52). The short-term changes in body weight were most likely related to changes in fluid balance. The overall weight gain in the control patients over the course of the one-year study was most likely related to increased body fat due to the glucose load inherent in dextrose-based solutions. The lack of weight gain in Extraneal patients may suggest a benefit of Extraneal in reducing weight gain due to excess glucose load. In this same study, there was a lower incidence of adverse events for peripheral edema (defined as 4+ edema), suggesting the possibility of better fluid management with Extraneal.

In order to assess whether Extraneal had any impact on quality of life, as compared to Dianeal, the Kidney Disease Quality of Life (KDQoL) Questionnaire was administered during Study RD-97-CA-131.

For patients who completed both the Baseline and the Week 52 KDQoL forms (N=25 Control, N=41 Extraneal), the overall scores for the Symptom/Problem items did not change significantly from Baseline to Week 52 within either treatment group. Furthermore, at the item level, no statistical differences were detected when the mean changes in scores were compared between treatment groups.

There were some KDQoL Symptom/Problem items for which the differences in change from Baseline to Week 52 between treatment groups exceeded 5 points. There was a clinically meaningful difference favoring the Extraneal Group in 10 items while there was a clinically meaningful difference favoring the Control Group in 5 items. Neither group had an advantage in the other 20 items.

When asked to compare their health in general now versus 1 year ago, a significantly greater (p=0.030) percentage of patients in the Extraneal Group (30%) responded that their health was "much better now than 1 year ago" compared to patients in the Control Group (4%).

7.2 RISKS

Incidences of adverse events, related events, and serious events were similar in Extraneal and dextrose treated patients.

In patients treated with Extraneal, the most common adverse events were peritonitis (26.4%), upper respiratory infection (15.0%), exit site infection (14.8%), hypertension (12.6%), anemia (11.2%), and rash (10.1%). With the exception of rash, the incidence of these adverse events was comparable to that observed in the control group.

The incidence of rash was higher among Extraneal patients compared with control (10.1 vs. 4.6%). However, the overall incidence of Skin system events (27.0% Extraneal, 22.5% control) was not significantly different between the two groups (p=0.764). Most rash events were mild or moderate in severity, appeared during the first 3 weeks of therapy, and often resolved even with continued use of Extraneal.

There were no reports of anaphylaxis, Stevens-Johnson syndrome or other serious immune-mediated reactions associated with skin rash.

Events reported with an incidence differing by greater than 3% or more between treatment groups included rash and hypertension reported more frequently with Extraneal and hypotension and hypokalemia reported more frequently with control patients:

Rash	10.1% Extraneal,	4.6% Control
Hypertension	12.6% Extraneal,	8.4% Control
Hypotension	6.5% Extraneal,	10.7% Control
Hypokalemia	6.9% Extraneal,	10.7% Control

Observational data on mortality did not show any statistically significant differences in survival time between groups and no deaths in either treatment group were considered related to study drug.

Laboratory evaluations demonstrated slight declines in mean sodium and chloride values in Extraneal patients, but the mean sodium values remained within normal limits. The mean chloride levels were consistently slightly below normal. These decreases are likely related to a dilutional effect caused by elevated blood levels of icodextrin and its metabolites. This is further supported by increases in mean osmolality values. Mean alkaline phosphatase levels were elevated in the Extraneal population, but remained within normal limits. No associated increases in liver function tests were observed. The overall changes in laboratory values were not clinically meaningful.

7.3 OVERALL CONCLUSION

The overall benefit/risk profile of Extraneal is summarized in **Table 7A**.

Table 7A: Benefits and Risks of Extraneal

BENEFITS	RISKS
• Increased net Ultrafiltration for single long dwell prescriptions • Reduced percentage of patients with negative net UF • Increased peritoneal creatinine clearance for single long dwell prescriptions • Increased peritoneal urea nitrogen or urea clearance for single long dwell prescriptions • Potential benefit in reducing weight gain and edema • 30% of patients in long-term study reported improved quality of life compared to a year ago versus 4% of control patients	• Most events were mild or moderate in severity and profile similar to active control • Skin adverse events (rash) most frequent related events • Slight changes in alkaline phosphatase, sodium, chloride with no known clinical relevance

In conclusion, the clinical studies in this NDA clearly demonstrate that patients treated with Extraneal have a significantly improved ultrafiltration compared with patients treated with either 1.5% or 2.5% dextrose solutions. Extraneal also significantly reduced the percentage of patients with negative net UF across these dextrose concentrations. Extraneal significantly enhanced waste solute clearance as compared to 1.5% and 2.5% dextrose solutions. The safety profile of Extraneal was comparable to currently marketed dextrose-based dialysis solutions. Thus, Extraneal is optimally suited for use as a single daily exchange for the long dialysis dwell.

8.0 PROPOSED LABELING

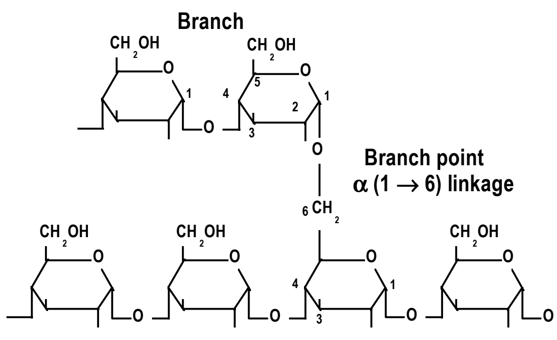
8.1 Package Insert

EXTRANEAL™

(7.5% Icodextrin) Peritoneal Dialysis Solution

DESCRIPTION

EXTRANEAL™ (7.5% Icodextrin) Peritoneal Dialysis Solution is a peritoneal dialysis solution containing the colloid osmotic agent icodextrin. Icodextrin is a starch derived, water soluble glucose polymer linked by alpha (1-4) and alpha (1-6) glucosidic bonds with a weight average molecular weight between 12,000 and 20,000 Daltons and a number average molecular weight between 5,000 and 6,500 Daltons. The representative structural formula of icodextrin is:



Each 1 liter of Extraneal contains:

Icodextrin	75.0 g
Sodium Chloride	5.4 g
Sodium Lactate	4.5 g
Calcium Chloride	257 mg
Magnesium Chloride	51 mg

Electrolyte content per 1 liter:

Sodium	132 mEq/l
Calcium	3.5 mEq/l
Magnesium	0.5 mEq/l
Chloride	96 mEq/l
Lactate	**40 mEq/l**

Water for Injection, USP qs
HCl/NaOH may have been used to adjust pH
Extraneal contains no bacteriostatic or antimicrobial agents.
Theoretical osmolarity: 285-288 mOsm/L; pH=5.2
Extraneal is available for intraperitoneal administration only as a sterile, nonpyrogenic, clear solution in 1.5 L, 2.0 L and 2.5 L Ambu-Flex III™ and Ultrabag™ containers. The container systems are composed of polyvinyl chloride.

CLINICAL PHARMACOLOGY

Mechanism of Action

Extraneal is an isosmotic peritoneal dialysis solution containing glucose polymers (icodextrin) as the primary osmotic agent. Icodextrin functions as a colloid osmotic agent to achieve sustained ultrafiltration during long peritoneal dialysis dwells. Icodextrin acts in the peritoneal cavity by exerting osmotic pressure across small intercellular pores resulting in a steady rate of transcapillary ultrafiltration throughout the dwell. Extraneal also contains electrolytes to help normalize electrolyte balance and lactate to help normalize acid-base status.

Pharmacokinetics of Icodextrin

Absorption

Absorption of icodextrin from the peritoneal cavity follows zero-order kinetics consistent with convective transport via peritoneal lymphatic pathways. In a single-dose pharmacokinetic study using Extraneal, a median of 40.1% (60.2 g) of the instilled icodextrin was absorbed from the peritoneal solution during a 12-hour dwell. Plasma levels of icodextrin rose during the dwell and declined after the dwell was drained, consistent with a one-compartment model with zero order absorption and first order elimination. Peak plasma concentrations (median C_{peak} = 2.23 g/L) were observed at the end of the long dwell exchange (median T_{max} = 12.7 hours) with plasma levels returning to baseline values within 3 to 7 days following cessation of icodextrin administration. Icodextrin had a plasma half-life of 14.7 hours and a median clearance rate of 1.08 L/hr. The mean steady-state plasma levels of icodextrin predicted from the above parameters (5.26 g/L) corresponded very closely to the stable plasma icodextrin values observed during long-term administration. In multidose studies, steady-state levels of icodextrin were achieved within one week and returned to baseline within one week after discontinuation of Extraneal use.

Metabolism

Icodextrin is metabolized by alpha-amylase into oligosaccharides with a lower degree of polymerization (DP), including maltose (DP_2), maltotriose (DP_3), maltotetraose (DP_4), and higher molecular weight species. In a single dose study, DP_2, DP_3 and DP_4 showed a progressive rise in plasma concentrations with a profile similar to that for total icodextrin, with peak values reached by the end of the dwell and declining thereafter. Only very small increases in blood levels of larger polymers were observed. Steady-state plasma levels of icodextrin metabolites were achieved within one week and stable plasma levels were observed during long-term administration. Some degree of metabolism of icodextrin occurs intraperitoneally with a progressive rise in the concentration of the smaller polymers in the dialysate during the 12-hour dwell.

Elimination

Icodextrin undergoes renal elimination in direct proportion to the level of residual renal function ($r=0.824$ vs creatinine clearance, $p<0.01$). In nine patients with residual renal function (mean creatinine clearance: 5.0 ± 1.5 ml/min), the average daily urinary excretion of icodextrin was 473 ± 77 mg per ml of creatinine clearance. Diffusion of the smaller icodextrin metabolites from plasma into the peritoneal cavity is also possible after systemic absorption and metabolism of icodextrin.

Special Populations

Geriatrics

In clinical studies of Extraneal in which plasma levels of icodextrin and its metabolites were measured, 95 patients were aged 65 and older. No apparent differences in plasma levels were observed in patients aged 65 and older as compared to patients under age 65.

Gender and Race

Although no specific studies were conducted to evaluate the differences between gender and race within the clinical trial data for icodextrin, no known differences have been detected.

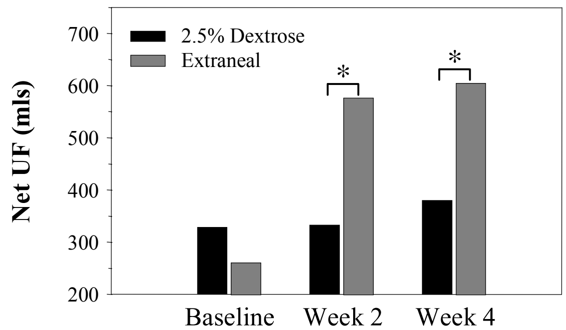
Pharmacodynamics and Clinical Effects

Extraneal has demonstrated efficacy as a peritoneal dialysis solution in clinical trials of approximately 400 patients studied with end-stage renal disease (ESRD).

Ultrafiltration, Urea and Creatinine Clearance, Negative Net Ultrafiltration

In active controlled trials from one to six months in duration, Extraneal used once daily for the long dwell in either continuous ambulatory peritoneal dialysis (CAPD) or ambulatory peritoneal dialysis (APD) therapy resulted in higher net ultrafiltration and clearances when compared with 2.5% dextrose solutions. In 175 CAPD patients randomized to Extraneal (N=90) or 2.5% dextrose solution (N=85) for the 8-15 hour overnight dwell for one month, mean net ultrafiltration for the overnight dwell was significantly greater for the Extraneal group compared to the 2.5% dextrose group when evaluated at weeks 2 and 4 (Figure 1).

Figure 1 - Mean Net Ultrafiltration for the Overnight Dwell (RD-97-CA-130)

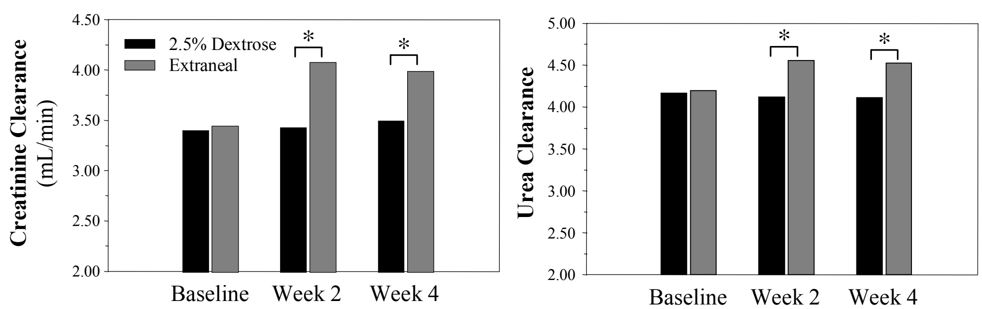


*P<0.001 for mean change from baseline

In 39 APD patients randomized to Extraneal or 2.5% dextrose solution for the long, daytime dwell (10-17 hrs) for three months, the average net ultrafiltration reported during the treatment period was 278 ± 43 ml for the Extraneal group and –138 ± 81 ml for the dextrose group (P<0.001).

Mean creatinine and urea nitrogen clearances were significantly greater for Extraneal as compared with 2.5% dextrose in CAPD patients at weeks 2 and 4 (Figure 2) and in APD patients at weeks 6 and 12 (P<0.001).

Figure 2 – Mean Creatinine and Urea Clearance for the Overnight Dwell (RD-97-CA-130)



*P<0.001 for mean change from baseline

*P<0.01 for mean change from baseline

Extraneal resulted in a significant decrease in the percentage of patients with negative net UF during long peritoneal dialysis dwells (10-17 hrs). When compared to 2.5% dextrose solution, the percentage of patients who were unable to achieve positive or zero ultrafiltration was significantly lower for patients using Extraneal for the long dwell in both CAPD and APD.

Long-term (12 month) Use

A randomized 12-month safety study (N=287) evaluated a single daily exchange of Extraneal for the 8 to 16-hour dwell in ESRD patients using CAPD or APD. One hundred seventy-five (175) patients were randomized to Extraneal and 112 patients to 2.5% dextrose.

Body Weight: *Long-term use (12 months) of Extraneal resulted in maintenance of stable body weight compared to a mean weight gain of 2.3 kg in the 2.5% dextrose group. The lack of weight gain observed in the Extraneal group may be related to a reduction in the glucose load during long dwells.*

Fluid Balance: Significantly fewer patients receiving Extraneal reported edema at Weeks 26 and 39 during the 12-month study when compared to patients on 2.5% dextrose (20% vs 35%). Overall, 17.9% of patients in the control group reported peripheral edema as compared to 6.3 % in the Extraneal group.

Peritoneal Membrane Transport Characteristics: *After one year of treatment with Extraneal during the long dwell exchange, there were no differences in membrane transport characteristics for urea and creatinine. There was a slight increase in the mass transfer area coefficient (MTAC) for glucose at one year, but it was not different from the change in MTAC in patients receiving treatment with 2.5% dextrose solution for the long dwell.*

Quality of Life: *Quality of life in the 12-month study was assessed by the Kidney Disease Quality of Life (KDQoL) evaluation. When asked to evaluate their general health at study completion, versus their baseline assessment, a significantly greater percentage of patients in the*

Extraneal group (30%) responded that their health was "much better now than one year ago" compared to the Control group (4%) (p<0.03).

INDICATIONS AND USAGE

Extraneal is indicated for a single daily exchange for the long (8 – 16 hour) dwell during continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD) for the management of chronic renal failure.

In clinical studies, Extraneal demonstrated enhanced ultrafiltration and creatinine and urea clearances when compared to 2.5% dextrose solutions. The percentage of patients with net negative ultrafiltration was significantly reduced with Extraneal compared to 2.5% dextrose (See CLINICAL PHARMACOLOGY –Pharmacodynamics and Clinical Effects).

CONTRAINDICATIONS

Extraneal is contraindicated in patients with a known allergy to cornstarch or icodextrin or in patients with glycogen storage disease.

WARNINGS

Not for intravenous injection.

PRECAUTIONS

General

Peritoneal Dialysis Related

All peritoneal dialysis solutions, including Extraneal, should be used with caution in patients with a history of abdominal surgery within thirty days of commencement of therapy, abdominal fistulae, tumors, open wounds, hernia or other conditions which compromise the integrity of the abdominal wall, abdominal surface or intra-abdominal cavity. Caution should also be used in patients with conditions that preclude normal nutrition, patients with impaired respiratory function, and patients with potassium deficiency.

Aseptic technique should be employed throughout the peritoneal dialysis procedure to reduce the possibility of infection. If peritonitis occurs, the choice and dosage of antibiotics should be based upon the results of culture and sensitivity of the isolated organisms. Prior to identification of involved organisms, broad-spectrum antibiotics may be indicated.

Patient's volume status should be carefully monitored to avoid hyper- or hypovolemia and potentially severe consequences including congestive heart failure, volume depletion and hypovolemic shock. An accurate fluid balance record must be kept and the patient's body weight monitored.

Significant losses of protein, amino acids, and water-soluble vitamins may occur during peritoneal dialysis. The patient's nutritional status should be monitored and replacement therapy provided as necessary.

Extraneal solution should be inspected for clarity, absence of particulate matter and container integrity. Solutions, which are cloudy, contain particulate matter, or evidence of leakage should not be used.

Treatment should be initiated and monitored under the supervision of a physician knowledgeable in the management of patients with renal failure.

Insulin dependent diabetes mellitus

Patients with insulin dependent diabetes may require modification of insulin dosage following initiation of treatment with Extraneal. Appropriate monitoring of blood glucose should be performed and insulin dosage adjusted if needed (*See Drug /Laboratory Test Interactions)*.

Information for Patients

Patients should be instructed to inspect each container of Extraneal solution for clarity, particulate matter, color and integrity of the container prior to use. Solutions should not be used if they are cloudy, discolored, contain visible particulate matter or if they have evidence of leaking containers.

Aseptic technique should be employed throughout the procedure.

To reduce possible discomfort during administration, patients should be instructed that solutions may be warmed to 37°C (98°F) prior to use. Only dry heat should be used. It is best to warm solutions within the overwrap. To avoid contamination, solutions should not be immersed in water for warming. Do not use a microwave oven to warm Extraneal. Heating the solution above 45°C (113°F) may be detrimental to the solution. (*See Directions for Use)*

Additional information for patients is provided at the end of the labeling.

Laboratory Tests

Serum Electrolytes

Decreases in serum sodium and chloride have been observed in patients using Extraneal. The declines in serum sodium and chloride may be related to dilution resulting from the presence of icodextrin metabolites in plasma. Although these decreases have been regarded as clinically unimportant, monitoring of the patients' serum electrolyte levels as part of routine blood chemistry testing is recommended.

Extraneal does not contain potassium. Evaluation of serum potassium should be made prior to administering potassium chloride to the patient.

Alkaline Phosphatase

An increase in mean serum alkaline phosphatase has been observed in clinical studies of ESRD patients receiving Extraneal. No associated increases in liver function tests were observed. Serum alkaline phosphatase levels did not show evidence of progressive increase over a 12-month study period. Levels returned to normal approximately two weeks after discontinuation of Extraneal.

Drug Interactions

General
No clinical drug interaction studies were performed. No evaluation of Extraneal's effects on the cytochrome P450 system was conducted. As with other dialysis solutions, blood concentrations of dialyzable drugs may be reduced by dialysis. Dosage adjustment of concomitant medications may be necessary. In patients using cardiac glycosides, plasma levels of calcium, potassium and magnesium must be carefully monitored.

Insulin

A clinical study in 6 insulin dependent diabetic patients demonstrated no effect of Extraneal on insulin absorption from the peritoneal cavity or on insulin's ability to control blood glucose when insulin was administered intraperitoneally with Extraneal. However, appropriate monitoring *(See Drug /Laboratory Test Interactions)* of blood glucose should be performed when initiating Extraneal in diabetic patients and insulin dosage should be adjusted if needed *(See Precautions)*.

Heparin

No human drug interaction studies with heparin were conducted. In vitro studies demonstrated no evidence of incompatibility of heparin with Extraneal.

Antibiotics

No human drug interaction studies with antibiotics were conducted. In vitro studies evaluating the minimum inhibitory concentration (MIC) of vancomycin, cefazolin, ampicillin, ampicillin/flucoxacillin, ceftazidime, gentamicin, and amphotericin demonstrated no evidence of incompatibility of these antibiotics with Extraneal. *(See Dosage and Administration)*

Drug/Laboratory Test Interactions

Blood Glucose

Blood glucose measurement must be done with a glucose specific method to prevent maltose interference with test results. Glucose dehydrogenase pyrroloquinolinequinone (GDH PQQ) based methods should not be used.

Serum Amylase

An apparent decrease in serum amylase activity has been observed in patients administered Extraneal. Preliminary investigations indicate that icodextrin and its metabolites interfere with enzymatic based amylase assays, resulting in inaccurately low values. This should be taken into account when evaluating serum amylase levels for diagnosis or monitoring of pancreatitis in patients using Extraneal.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Icodextrin did not demonstrate evidence of mutagenic potential in *in vitro* or *in vivo* studies performed. Long-term animal studies to evaluate the carcinogenic potential of Extraneal or icodextrin have not been conducted. Icodextrin is derived from maltodextrin, a common food ingredient that is generally regarded as safe.

A preliminary fertility study in rats revealed slightly low epididymal weights in parental males in the high dose group (1.5 g/kg/day), as compared to Control. Toxicological significance of this finding was not evident as no other reproductive organs were affected and all males were of proven fertility. Studies on the effects of icodextrin on male and female fertility have not been performed.

Pregnancy

Pregnancy Category C

Complete animal reproduction studies have not been conducted with Extraneal or icodextrin. Thus it is not known whether icodextrin or Extraneal solution can cause fetal harm when administered to a pregnant woman or affect reproductive capacity.
Extraneal should only be utilized in pregnant women when the need outweighs the potential risks.

A preliminary study of the effects of icodextrin on the fertility and pregnancy in rats demonstrated no effects of treatment with icodextrin on mating performance, fertility, litter response, embryo-fetal survival, or fetal growth and development.

Nursing Mothers

It is not known whether icodextrin or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Extraneal is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

No formal studies were specifically carried out in the geriatric population. However, approximately 25% of the patients in clinical studies of Extraneal were age 65 or older, with ~ 4% of patients age 75 or older. No overall differences in safety or effectiveness were observed between these patients and patients under age 65. Although clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Adverse Reactions from Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Significance of Adverse Reaction Data Obtained from Clinical Trials

Extraneal was studied in controlled clinical trials of 366 patients with end-stage renal disease, including 60 patients exposed for 6 months and 155 patients exposed for one year. The population was 18-93 years of age, 56% male and 44% female, 73% Caucasian, 18% Black, 4% Asian, 3% Hispanic and included patients with the following comorbid conditions: 26.8% diabetes, 49.3% hypertension and 23.1% hypertensive nephropathy. All patients received a single daily exchange of Extraneal for the long dwell (8-16 hours).

Rash was the most frequently occurring icodextrin-related adverse event (5.5%, Extraneal; 1.7% Control). A listing of adverse events reported in these same clinical studies, regardless of causality, occurring in ≥ 5% of patients is presented in Table 1.

Additional adverse reactions that were possibly, probably or definitely related to Extraneal with an incidence of less than 5% within each body system were as follows:
Body as a Whole --Pain neck, PD catheter dysfunction, Face edema, Bloody effluent; *Cardiovascular*--Postural hypertension, tachycardia, Cardiovascular disease, Syncope, Cerebrovascular accident, Palpitations; *Hematologic and Lymphatic*--Leukocytosis, Eosinophilia; *Digestive*--Anorexia, Liver function abnormal, Constipation, Gastrointestinal disorder, Flatulence, Gastritis, Intestinal obstruction, Stomach ulcer, Gastroenteritis, Stool abnormal; *Metabolic and Nutrition*-- Dehydration, Hypovolemia, Hypochloremia, Hypomagnesemia, Weight increase, Increase alkaline phosphatase, Hyponatremia, Hypoglycemia, Increase SGOT, Increase SGPT, Decrease weight, Decrease ultrafiltration, Increase Creatinine; *Musculoskeletal--M*yalgia, Cramps Leg, Cramping, and Bone Pain; *Nervous*--Paresthesia, Dry mouth, Anxiety, Hyperkinesia, Nervousness, Abnormal thinking, Insomnia, Somnolence, Depression; *Respiratory*--Lung disorder, Lung edema, Hiccup, Rhinitis, *Skin*--Exfoliative dermatitis, Nail disorder, psoriasis, Rash macular papular, Eczema, Furunculosis, Rash vesicle bullar, Skin discoloration, Dry skin, Skin ulcer, Urticaria;*Special Senses*--Taste loss, Taste perversion; *Urogenital*—Pain kidney, Edema scrotum.

Table 1 - Adverse Experiences in >5 % of Patients

	Extraneal N = 366	**Control N=347**
	N (%)	N (%)
Body in General		
Peritonitis	130 (26.4)	88 (25.4)
Exit Site Infection	73 (14.8)	58 (16.7)
Pain	48 (9.7)	43 (12.4)
Headache	43 (8.7)	23 (6.6)
Pain Abdominal	39 (7.9)	20 (5.8)
Flu Syndrome	35 (7.1)	21 (6.1)
Injury Accidental	31 (6.3)	14 (4.0)
Asthenia	28 (5.7)	27 (7.8)
Lab Test Abnormal	25 (5.1)	12 (3.5)
Pain Chest	25 (5.1)	12 (3.5)
Pain Back	22 (4.5)	18 (5.2)
Infect	21 (4.3)	19 (5.5)
Cardiovascular		
Hypertension	62 (12.6)	29 (8.4)
Hypotension	32 (6.5)	37 (10.7)
Digestive		
Diarrhea	40 (8.1)	33 (9.5)

Nausea	35 (7.1)	17 (4.9)
Nausea vomit	25 (5.1)	21 (6.1)
Dyspepsia	25 (5.1)	13 (3.7)
Vomit	22 (4.5)	19 (5.5)
Hematologic & Lymphatic		
Anemia	55 (11.2)	39 (11.2)
Metabolic and Nutrition		
Hypokalemia	34 (6.9)	37 (10.7)
Hypoproteinemia	34 (6.9)	32 (9.2)
Hypervolemia	28 (5.7)	20 (5.8)
Edema	28 (5.7)	17 (4.9)
Hyperphosphatemia	25 (5.1)	26 (7.5)
Hyperglycemia	25 (5.1)	12 (3.5)
Edema Periph	18 (3.7)	29 (8.4)
Musculoskeletal		
Arthralgia	31 (6.3)	27 (7.8)
Nervous		
Dizziness	27 (5.5)	19 (5.5)
Respiratory		
Upper Res Infection	74 (15.0)	46 (13.3)
Cough increase	35 (7.1)	13 (3.7)
Dyspnea	26 (5.3)	24 (6.9)
Skin		
Rash	50 (10.1)	16 (4.6)
Pruritus	27 (5.5)	23 (6.6)
Skin Disorder	11 (2.2)	18 (5.2)

Peritoneal Dialysis Related

Adverse events common to the treatment modality of peritoneal dialysis including peritonitis, infection around the catheter, fluid and electrolyte imbalance, and pain were observed at a similar frequency with Extraneal and Controls *(See **Precautions**)*.

Changes in Alkaline Phosphatase and Serum Electrolytes

An increase in mean serum alkaline phosphatase has been observed in clinical studies of ESRD patients receiving Extraneal. No associated increases in liver function tests were observed. Serum alkaline phosphatase levels did not show evidence of progressive increase over a 12-month study period. Levels returned to normal approximately two weeks after discontinuation of Extraneal.

Decreases in serum sodium and chloride have been observed in patients using Extraneal. The declines in serum sodium and chloride may be related to dilution resulting from the presence of icodextrin metabolites in plasma. Although these decreases have been regarded as clinically nonsignificant, monitoring of the patients serum electrolyte levels as part of routine blood chemistry testing is recommended.

DRUG ABUSE AND DEPENDENCE

There has been no observed potential of drug abuse or dependence with Extraneal.

OVERDOSAGE

No data is available on experiences of overdosage with Extraneal. Overdosage of Extraneal may result in higher levels of serum icodextrin and metabolites. It is unknown what symptoms may be caused from exposure in excess of those observed in clinical trials. In the event of overdosage with Extraneal, continued peritoneal dialysis with glucose-based solutions should be provided.

DOSAGE AND ADMINISTRATION

Extraneal is intended for intraperitoneal administration only. It should be administered only as a single daily exchange for the long dwell in continuous ambulatory peritoneal dialysis or automated peritoneal dialysis. The recommended dwell time is 8 to 16 hours.

Patients should be carefully monitored to avoid under or over hydration. An accurate fluid balance record must be kept and the patient's body weight monitored to avoid over or under hydration and potentially severe consequences including congestive heart failure, volume depletion and hypovolemic shock.

Aseptic technique should be used throughout the peritoneal dialysis procedure.

To reduce possible discomfort during administration, patients should be instructed that solutions may be warmed to 37°C (98°F) prior to use. Only dry heat should be used. To avoid contamination, solutions should not be immersed in water for warming. Do not use a microwave oven to warm Extraneal. Heating the solution above 45°C (113°F) may be detrimental to the solution. (*See Directions for Use)*

Extraneal should be administered over a period of 10-20 minutes at a rate that is comfortable for the patient.

Parenteral drug products, including Extraneal, should be visually inspected for particulate matter, leakage and discoloration prior to use. Should these be present, discard product; do not use.

Following use, the drained fluid should be inspected for the presence of fibrin or cloudiness, which may indicate the presence of an infection.

Addition of Insulin

Addition of insulin to Extraneal was evaluated in 6 insulin dependent diabetic patients undergoing CAPD for end stage renal disease. No interference of Extraneal on insulin absorption from the peritoneal cavity or on insulin's ability to control on blood glucose was observed (*See Drug /Laboratory Test Interactions)*. Appropriate monitoring of blood glucose should be performed when initiating Extraneal in diabetic patients and insulin dosage adjusted if needed (*See Precautions)*.

Addition of Heparin
No human drug interaction studies with heparin were conducted. In vitro studies demonstrated no evidence of incompatibility of heparin with Extraneal.

Addition of Antibiotics

No formal clinical drug interaction studies have been performed. In vitro compatibility studies with Extraneal and the following antibiotics have demonstrated no effects with regard to minimum inhibitory concentration (MIC): vancomycin, cefazolin, ampicillin/flucoxcillin, ceftazidime, gentamicin, and amphotericin.
Patients undergoing peritoneal dialysis should be under careful supervision of a physician experienced in the treatment end-stage renal disease with peritoneal dialysis. It is recommended that patients being placed on peritoneal dialysis should be appropriately trained in a program that is under supervision of a physician. Training materials are available from Baxter Healthcare Corporation, Deerfield, IL 60015, USA.

Directions for Use

For complete CAPD and APD system preparation, see directions accompanying ancillary equipment.

Aseptic technique should be used.

Warming

For patient comfort, Extraneal can be warmed to 37°C (98°F). Only dry heat should be used. It is best to warm solutions within the overwrap. Do not immerse Extraneal in water for warming. Do not use a microwave oven to warm Extraneal. Heating above 45°C (113°F) may be detrimental to the solution.

To Open

To open, tear the over wrap down at the slit and remove the solution container. Some opacity of the plastic, due to moisture absorption during the sterilization process, may be observed. This does not affect the solution quality or safety and may often leave a slight amount of moisture within the overwrap.

Inspect for Container Integrity

Inspect the container for signs of leakage and check for minute leaks by squeezing the container firmly.

Adding Medications

Some drug additives may be incompatible with Extraneal. See DOSAGE AND ADMINISTRATION section for additional information. If the re-sealable rubber plug on the medication port is missing or partly removed, do not use the product if medication is to be added.

1. Prepare medication port site.
2. Using a syringe with a 1-inch long, 25 to 19-gauge needle, puncture the medication port and inject additive.
3. Reposition container with container ports up and evacuate medication port by squeezing and tapping it.
4. Mix container thoroughly.

Preparation for Administration

1. Place Extraneal on flat surface or suspend from support (depending on ancillary equipment).
2. Remove protector from outlet port on container.
3. Attach solution transfer set. Refer to complete instructions with ancillary equipment or transfer set.
4. Discard any unused portion.

HOW SUPPLIED

Extraneal (7.5% icodextrin) Peritoneal Dialysis Solution is available in the following containers and fill volumes:

Container	**Fill Volume**	**NDC**
Ultra-Bag	1.5 L	NDC 0941-0679-51
Ultra-Bag	2.0 L	NDC 0941-0679-52
Ultra-bag	2.5 L	NDC 0941-0679-53
Ambu-Flex	1.5 L	NDC 0941-0679-45
Ambu-Flex	2.0 L	NDC 0941-0679-47

Ambu-Flex	2.5 L	NDC 0941-0679-48

Each liter of Extraneal contains 75 grams of icodextrin in an electrolyte solution with 40 mEq/l lactate.

Extraneal should be stored at controlled room temperature 68–77°F (20–25°C). Store in moisture barrier overwrap in carton until ready to use.

Avoid excessive heat (104°F/40°C) and protect from freezing.

Rx Only

8.2 INFORMATION FOR PATIENTS

Questions and Answers About

Extraneal™
(generic name = 7.5% icodextrin peritoneal dialysis solution)

What is the Most Important Information I should Know About Extraneal?

Extraneal (pronounced "X-tra-neel") is used for the long dwell exchange (8 to 16 hours) in peritoneal dialysis. You should use Extraneal only for this exchange and not more than one exchange in 24 hours.

You should not use Extraneal if you are allergic to cornstarch, or have had an allergic reaction to icodextrin. Potentially serious skin rash may occur with Extraneal. If you develop a rash, call your doctor immediately.

As with all peritoneal dialysis solutions, it is important to make sure the solution is clear, and that the bag is not leaking before use. Always use sterile technique when using Extraneal. Report any symptoms of infection (pain, redness, heat) to your doctor immediately.

What is Extraneal?

Extraneal is a sterile peritoneal dialysis solution. Extraneal contains icodextrin in place of glucose found in other peritoneal dialysis solutions. Icodextrin is made from cornstarch. It draws fluid and wastes from your bloodstream into your peritoneal cavity. The fluids and wastes are removed from your body when the Extraneal solution is drained.

Who should not use Extraneal?

Do not use Extraneal if you are allergic to icodextrin or cornstarch.

How Should I Use Extraneal?

Your doctor has prescribed Extraneal for your long dwell (8 to16 hours) peritoneal dialysis exchange. You should use Extraneal for this exchange only and not more than one exchange in 24 hours.

It is very important that you make sure that you follow the steps shown to you in your peritoneal dialysis training. All surfaces and connecting parts must be clean to avoid serious infection.

Always check to make sure the bags are not leaking and that the solution is clear and has not expired, before using. Make sure that the solution is clear and does not contain particles. Do not use bags that are cloudy, leaking or contain particles. Do not use Extraneal after the expiration date shown on the carton and product label.

You must use sterile technique while performing a dialysis exchange.

To make using Extraneal more comfortable, it can be warmed in the overpouch to 98.6°F/37C before use. This should be done using dry heat only. To avoid increased risk of infection, do not place Extraneal in hot water to heat the bags. Do not microwave Extraneal.

Extraneal should be instilled over 10 to 20 minutes at a rate that is comfortable for you. When draining the fluid after the dwell, always check the drained fluid for cloudiness or fibrin. Cloudy drained fluid may indicate an infection.

When your doctor prescribes Extraneal, he/she should instruct you to carefully monitor your fluid balance. You must keep an accurate fluid record and carefully monitor your body weight to avoid over or under hydration, which may have serious effects such as heart failure and shock.

If you take medications for blood pressure or insulin for diabetes, you doctor may need to adjust these medications when you begin using Extraneal. Your doctor may also instruct you to have certain blood tests done. It is important that you follow your doctor's orders.

Talk to your doctor before adding any other medications to Extraneal.

What are the side effects of Extraneal?

Rash In some patients Extraneal may cause a rash or itching and peeling of the skin that may start on the palms of hand and feet or affect other parts of the body. If you develop a rash or itching and peeling of your skin, you should tell your doctor immediately.

Other Side Effects As with other peritoneal dialysis solutions, you may experience side effects such as pain on infusion, muscle cramps, decreased appetite, nausea, vomiting, changes in blood pressure, fluid changes, and changes in electrolyte (e.g. sodium, potassium) levels. Infection (peritonitis) can also occur.

It is important that you tell your doctor immediately if you experience any symptoms.

How should I store Extraneal?

Extraneal should be stored at controlled room temperature 68 – 77°F (20 –25°C). Store in moisture barrier overpouch in carton until ready to use.
Avoid Excessive Heat (40°C/104°F).
Protect from freezing.

9.0 REFERENCES

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COMPARISON OF MORTALITY IN ALL PATIENTS ON DIALYSIS, PATIENTS ON DIALYSIS AWAITING TRANSPLANTATION, AND RECIPIENTS OF A FIRST CADAVERIC TRANSPLANT

ROBERT A. WOLFE, PH.D., VALARIE B. ASHBY, M.A., EDGAR L. MILFORD, M.D., AKINLOLU O. OJO, M.D., PH.D., ROBERT E. ETTENGER, M.D., LAWRENCE Y.C. AGODOA, M.D., PHILIP J. HELD, PH.D., AND FRIEDRICH K. PORT, M.D.

ABSTRACT

Background The extent to which renal allotransplantation — as compared with long-term dialysis — improves survival among patients with end-stage renal disease is controversial, because those selected for transplantation may have a lower base-line risk of death.

Methods In an attempt to distinguish the effects of patient selection from those of transplantation itself, we conducted a longitudinal study of mortality in 228,552 patients who were receiving long-term dialysis for end-stage renal disease. Of these patients, 46,164 were placed on a waiting list for transplantation, 23,275 of whom received a first cadaveric transplant between 1991 and 1997. The relative risk of death and survival were assessed with time-dependent nonproportional-hazards analysis, with adjustment for age, race, sex, cause of end-stage renal disease, geographic region, time from first treatment for end-stage renal disease to placement on the waiting list, and year of initial placement on the list.

Results Among the various subgroups, the standardized mortality ratio for the patients on dialysis who were awaiting transplantation (annual death rate, 6.3 per 100 patient-years) was 38 to 58 percent lower than that for all patients on dialysis (annual death rate, 16.1 per 100 patient-years). The relative risk of death during the first 2 weeks after transplantation was 2.8 times as high as that for patients on dialysis who had equal lengths of follow-up since placement on the waiting list, but at 18 months the risk was much lower (relative risk, 0.32; 95 percent confidence interval, 0.30 to 0.35; $P<0.001$). The likelihood of survival became equal in the two groups within 5 to 673 days after transplantation in all the subgroups of patients we examined. The long-term mortality rate was 48 to 82 percent lower among transplant recipients (annual death rate, 3.8 per 100 patient-years) than patients on the waiting list, with relatively larger benefits among patients who were 20 to 39 years old, white patients, and younger patients with diabetes.

Conclusions Among patients with end-stage renal disease, healthier patients are placed on the waiting list for transplantation, and long-term survival is better among those on the waiting list who eventually undergo transplantation. (N Engl J Med 1999;341:1725-30.)

IN patients with end-stage renal disease, successful renal allotransplantation improves the quality of life and increases survival, as compared with long-term dialysis treatment.[1-3] The survival advantage of renal transplantation varies among patients,[4-7] but this variability has not been well characterized. Most studies have not considered the fact that transplant recipients are derived from a highly selected subgroup of patients on dialysis who are deemed suitable candidates for transplantation. Patients on dialysis who are placed on the waiting list for cadaveric renal transplantation are on average younger and healthier and of higher socioeconomic status than those who are not selected.[8-10] Because of these selection factors, the survival of patients on dialysis who are awaiting transplantation is better than that of other patients on dialysis, even before renal transplantation.

The number of cadaveric organs available has not kept up with the increasing number of patients awaiting transplantation.[11] The rapid expansion of the recipient pool, particularly of high-risk patients, has increased the pressure on transplantation programs to devise appropriate selection criteria (e.g., age) to optimize the use of scarce organs. The present study was designed to compare survival of patients undergoing transplantation with survival of those awaiting transplantation.

METHODS

We used data from the U.S. Renal Data System for this study. From 1991 through 1996, 252,358 patients under the age of 70 years began treatment for end-stage renal disease in the United States. We excluded patients who were 70 years of age or older, because only about 1 percent of them received a cadaveric renal transplant; those whose race was listed as other than Asian, Native American, black, or white; and those for whom the cause of end-stage renal disease or the region they were from was not reported. Patients who received transplants without first undergoing dialysis were also excluded. The resulting study population included

From the U.S. Renal Data System Coordinating Center (R.A.W., V.B.A.) and the Departments of Biostatistics (R.A.W., V.B.A.), Internal Medicine (A.O.O., F.K.P.), and Epidemiology (F.K.P.), University of Michigan, Ann Arbor; Brigham and Women's Hospital, Boston (E.L.M.); the Department of Pediatric Nephrology, University of California Los Angeles, Los Angeles (R.E.E.); the National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Md. (L.Y.C.A.); and the University Renal Research Education Association, Ann Arbor, Mich. (P.J.H.). Address reprint requests to Dr. Wolfe at the University of Michigan, 315 W. Huron, Suite 240, Ann Arbor, MI 48103, or at bobwolfe@umich.edu.

TABLE 1. CHARACTERISTICS OF PATIENTS WITH END-STAGE RENAL DISEASE, 1991–1997.

CHARACTERISTIC	ALL PATIENTS ON DIALYSIS (N=228,552)	PATIENTS ON THE WAITING LIST (N=46,164)	RECIPIENTS OF CADAVERIC TRANSPLANTS (N=23,275)
		percent	
Age*			
0–19 yr	1.7	2.8	3.7
20–39 yr	17.0	31.2	33.6
40–59 yr	42.5	50.9	49.7
≥60 yr	38.8	15.0	13.0
Female sex	45.6	39.5	37.2
Race			
White	60.3	65.4	71.3
Black	34.7	28.6	23.6
Asian	3.1	4.4	3.9
Native American	1.9	1.7	1.2
Cause of end-stage renal disease			
Diabetes	44.7	32.9	31.2
Glomerulonephritis	12.5	22.0	23.0
Other	42.8	45.1	45.8

*The ages shown are the age at the time of the first treatment for end-stage renal disease in the group of all patients on dialysis (age limit, 69 years), the age at the time of initial placement on the waiting list for patients on the waiting list, and the age at transplantation for transplant recipients.

228,552 patients, of whom 46,164 had been placed on the waiting list for transplantation for the first time. Among these patients on the waiting list, 23,275 received a first cadaveric transplant by December 31, 1997.

Survival was analyzed as the time from initial placement on the waiting list to death, with data censored at the time of receipt of a first transplant from a living donor or on December 31, 1997. A time-dependent, nonproportional-hazards analysis was used to account for the fact that patients switched from the dialysis group to the transplantation group during follow-up. The analysis showed that mortality was higher in the transplantation group immediately after transplantation and then dropped below the rate in the dialysis group over the long term. We calculated the number of days between placement on the waiting list and the time at which the death rates became equal in the two groups as well as cumulative survival probabilities and the projected years of life, with adjustment for the time spent on the waiting list.[12] The analyses were adjusted for age, race, sex, cause of end-stage renal disease (glomerulonephritis, diabetes, or other causes), year of placement on the waiting list, time from first treatment for end-stage renal disease to placement on the waiting list, and geographic region. The analysis was conducted according to the intention to treat; therefore, patients were not dropped from the analysis if they were removed from the waiting list or if transplantation failed. Although some patients were on the waiting list at multiple centers and received more than one transplant, we only considered the time of the initial placement on the waiting list and the first transplantation. We analyzed subgroups of patients separately. In addition, we calculated standardized mortality ratios, adjusted for age, sex, race, and diabetes as the cause of end-stage renal disease,[13] to compare the death rates among the 46,164 patients on dialysis who were placed on the waiting list and the 23,275 recipients of cadaveric transplants with those among the entire group of 228,552 patients on dialysis; we used the death-rate tables of the U.S. Renal Data System for all U.S. patients on dialysis in 1997 as a reference.[11]

RESULTS

The percentages of blacks, Native Americans, women, and patients with diabetes were lower among patients who had been placed on the waiting list and recipients of cadaveric transplants than among the group of patients on dialysis as a whole (Table 1). The unadjusted annual death rates per 100 patient-

TABLE 2. ANNUAL DEATH RATES AND TOTAL NUMBERS OF DEATHS, 1991–1997.

VARIABLE	ALL PATIENTS ON DIALYSIS (N=228,552)		PATIENTS ON THE WAITING LIST (N=46,164)		RECIPIENTS OF CADAVERIC TRANSPLANTS (N=23,275)	
	RATE/100 PATIENT-YR	NO. OF DEATHS	RATE/100 PATIENT-YR	NO. OF DEATHS	RATE/100 PATIENT-YR	NO. OF DEATHS
All patients	16.1	84,713	6.3	4353	3.8	2436
Age*						
0–19 yr	3.6	257	2.2	31	0.9	21
20–39 yr	8.6	7,499	4.3	897	2.3	500
40–59 yr	13.3	30,935	6.5	2372	4.1	1293
≥60 yr	23.2	46,022	10.0	1053	7.4	622
Sex						
Male	16.2	45,366	6.3	2556	3.9	1590
Female	16.1	39,347	6.3	1797	3.5	846
Race						
White	19.3	55,786	7.5	2993	3.9	1859
Black	12.4	25,733	4.8	1168	3.4	478
Asian	9.9	1,783	3.0	108	2.6	64
Native American	13.3	1,411	6.5	84	4.7	35
Cause of end-stage renal disease						
Diabetes	19.9	44,916	10.8	2312	5.6	1091
Other	13.3	39,797	4.3	2041	3.0	1345

*The ages shown are the age at the time of the first treatment for end-stage renal disease in the group of all patients on dialysis (age limit, 69 years), the age at the time of initial placement on the waiting list for patients on the waiting list, and the age at transplantation for transplant recipients.

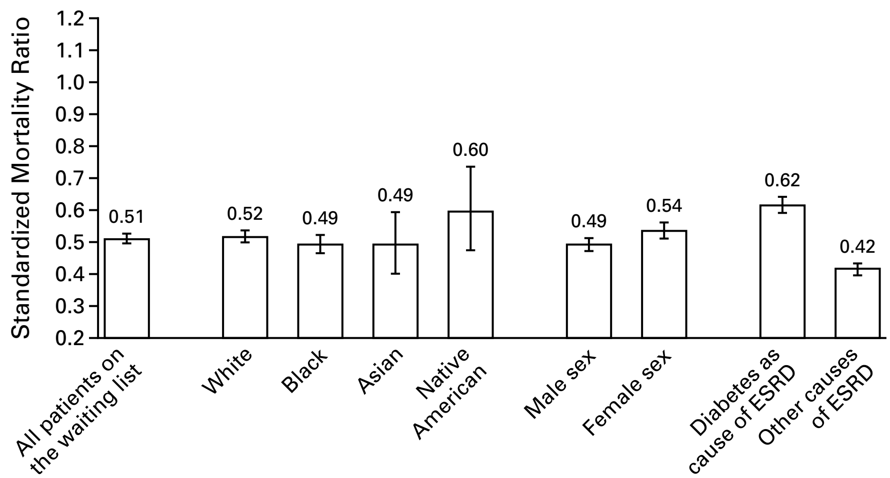

Figure 1. Standardized Mortality Ratios for Patients on the Waiting List for Renal Transplants, According to Race, Sex, and Diabetes as the Cause of End-Stage Renal Disease (ESRD), 1991–1997.

The reference groups were all patients on dialysis who were less than 70 years of age at the onset of end-stage renal disease and the corresponding subgroups classified according to race, sex, and diabetes as the cause of end-stage renal disease (relative risk of death, 1.0). The ratios were adjusted for age, race, sex, and diabetes as the cause of end-stage renal disease. I bars indicate 95 percent confidence intervals. $P<0.001$ for all comparisons.

years at risk for all patients on dialysis, patients on the waiting list, and transplant recipients were 16.1, 6.3, and 3.8, respectively (Table 2). The annual death rate for all patients on dialysis was 2.6 times as high as that for patients on the waiting list, and the annual death rate for patients on the waiting list was 1.7 times as high as that for transplant recipients. The total deaths in each group are also shown in Table 2.

The standardized mortality ratios, adjusted for age, race, sex, and diabetes as the cause of end-stage renal disease, for patients on the waiting list as compared with the corresponding group of all patients on dialysis who were younger than 70 years at the onset of end-stage renal disease (relative risk, 1.0) are shown in Figure 1.[13] The standardized mortality ratio was 49 percent lower (relative risk, 0.51; 95 percent confidence interval, 0.49 to 0.53; $P<0.001$) among patients on the waiting list and 69 percent lower (data not shown) among the recipients of cadaveric transplants. Thus, much of the large reduction in risk among the recipients of cadaveric transplants was most likely due to the selection of healthier patients for placement on the waiting list. The standardized mortality ratio was also significantly lower among each subgroup of patients on the waiting list (whites, blacks, Asians, Native Americans, female patients, male patients, those with diabetes, and those without diabetes) than among the corresponding subgroup of all patients on dialysis ($P<0.001$ for each comparison).

The relative risk of death among transplant recipients, as compared with patients on the waiting list, adjusted for age, sex, race, cause of end-stage renal disease, year of placement on the waiting list, and time from first treatment for end-stage renal disease to placement on the waiting list, is shown in Figure 2. Transplant recipients, including patients in whom transplantation was unsuccessful, were compared with patients on the waiting list who had equal lengths of follow-up since placement on the waiting list but who had not yet received a cadaveric transplant. The

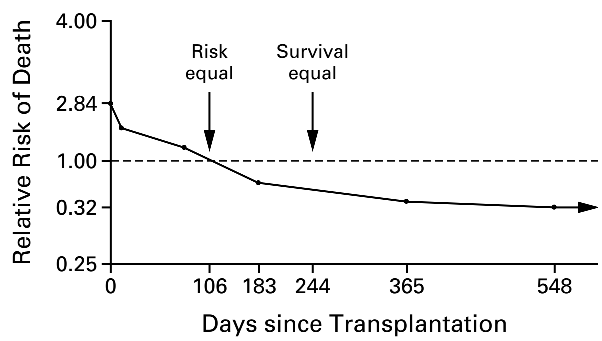

Figure 2. Adjusted Relative Risk of Death among 23,275 Recipients of a First Cadaveric Transplant.

The reference group was the 46,164 patients on dialysis who were on the waiting list (relative risk, 1.0). Patients in both groups had equal lengths of follow-up since placement on the waiting list. Values were adjusted for age, sex, race, cause of end-stage renal disease, year of placement on the waiting list, geographic region, and time from first treatment for end-stage renal disease to placement on the waiting list. The points at which the risk of death and the likelihood of survival were equal in the two groups are indicated. A log scale was used.

TABLE 3. OUTCOME AMONG RECIPIENTS OF FIRST CADAVERIC TRANSPLANTS, ACCORDING TO CHARACTERISTICS AT THE TIME OF INITIAL PLACEMENT ON THE WAITING LIST, 1991–1997.*

GROUP	RELATIVE RISK 18 MO AFTER TRANSPLANTATION (95% CI)†	P VALUE	TIME AT WHICH RISK OF DEATH EQUALS THAT IN REFERENCE GROUP	TIME AT WHICH LIKELIHOOD OF SURVIVAL EQUALS THAT IN REFERENCE GROUP	PROJECTED YEARS OF LIFE (IN REFERENCE GROUP) WITHOUT TRANSPLANTATION†‡	PROJECTED YEARS OF LIFE WITH TRANSPLANTATION‡
			days after transplantation			
All recipients of first cadaveric transplants	0.32 (0.30–0.35)	<0.001	106	244	10	20
Age						
0–19 yr	0.33 (0.12–0.87)	0.03	3	5	26	39
20–39 yr	0.24 (0.20–0.29)	<0.001	11	57	14	31
40–59 yr	0.33 (0.29–0.37)	<0.001	95	251	11	22
60–74 yr	0.39 (0.33–0.47)	<0.001	148	369	6	10
Sex						
Male	0.34 (0.30–0.38)	<0.001	110	255	10	19
Female	0.30 (0.26–0.34)	<0.001	94	220	11	23
Race						
Native American	0.50 (0.27–0.96)	0.04	123	304	9	14
Asian	0.43 (0.25–0.75)	0.003	161	673	15	23
Black	0.52 (0.44–0.62)	<0.001	109	305	13	19
White	0.28 (0.25–0.30)	<0.001	100	220	9	19
Cause of end-stage renal disease						
Diabetes	0.27 (0.24–0.30)	<0.001	57	146	8	19
Glomerulonephritis	0.39 (0.31–0.48)	<0.001	130	360	11	18
Other	0.38 (0.33–0.43)	<0.001	137	353	12	20
Age and diabetes status						
20–39 yr, no diabetes	0.38 (0.28–0.50)	<0.001	14	220	20	31
20–39 yr, diabetes	0.18 (0.14–0.23)	<0.001	10	35	8	25
40–59 yr, no diabetes	0.38 (0.33–0.43)	<0.001	126	356	12	19
40–59 yr, diabetes	0.27 (0.23–0.32)	<0.001	66	181	8	22
60–74 yr, no diabetes	0.37 (0.30–0.46)	<0.001	159	442	7	12
60–74 yr, diabetes	0.46 (0.34–0.61)	<0.001	89	247	5	8

*All analyses were adjusted for age, sex, race, cause of end-stage renal disease, year of placement on the waiting list, geographic region, and time from first treatment for end-stage renal disease to placement on the waiting list. CI denotes confidence interval.

†The reference group was the 46,164 patients on dialysis who were on the waiting list.

‡The starting point for the calculation was the time of initial placement on the waiting list.

risk of death among the transplant recipients during the first 2 weeks after transplantation was 2.8 times as high as that among the patients on the waiting list and remained elevated until 106 days after transplantation. After this time, the risk was lower among the transplant recipients, but the likelihood of survival did not become equal in the two groups until day 244, because of the initially higher risk among the transplant recipients. The long-term mortality risk for the transplant recipients was estimated to be 68 percent lower than that of the patients on the waiting list (relative risk, 0.32; 95 percent confidence interval, 0.30 to 0.35; P<0.001). The long-term risk was estimated on the basis of three to four years of follow-up.

The outcomes among the various subgroups of patients who received a cadaveric transplant are shown in Table 3. Overall, the projected years of life remaining were 10 for patients who remained on the waiting list and 20 for those who received a transplant. The greatest difference in long-term survival was found among patients who were 20 to 39 years old at the time of placement on the waiting list: those who underwent transplantation were projected to live almost 17 years longer than those who remained on the waiting list. Among the patients who were 60 to 74 years old, the cumulative survival rate improved after the first year after transplantation, with a projected increase in the life span of four years and a decrease in the long-term risk of death of 61 percent. When this subgroup was further subdivided into patients who were 60 to 64 years of age, those who were 65 to 69 years, and those who were 70 to 74 years, the projected increases in the life span were 4.3 years, 2.8 years, and 1.0 year, respectively. When the results were analyzed according to race, transplantation reduced the long-term relative risk of death more among Asians and whites than among Native Americans and blacks. However, in all four racial groups, transplantation significantly reduced the long-term risk of death, with initially higher mortality in the transplantation groups disappearing within less than half a year. The cumulative mortality rate was lower within 10 months after transplantation in all racial groups except Asians, who had the lowest mortality rate while receiving dialysis on the waiting list and for whom it required two years after transplantation for the mortality rate to return to this level.

The relative survival benefits of transplantation were similar for men and women, with the long-term risk of death decreasing by 66 percent and 70 percent, respectively, and the initially higher mortality disappearing within eight and seven months, respectively. The results were similar for the subgroups of patients with diabetes, glomerulonephritis, and other causes of end-stage renal disease. Among patients with diabetes who were on the waiting list, the annual mortality rate was close to 11 percent. Transplantation reduced the risk of death by 73 percent (relative risk, 0.27; 95 percent confidence interval, 0.24 to 0.30; $P<0.001$). When projected long-term survival after transplantation was analyzed according to the cause of end-stage renal disease, the greatest increase occurred among patients with diabetes, with a gain of more than 11 years, as compared with an increase of 7 years among those with glomerulonephritis and 8 years among those with other causes of end-stage renal disease.

Patients with diabetes and patients who were 20 to 39 years old, 40 to 59 years old, or 60 to 74 years old at the time of placement on the waiting list were examined to assess the benefit of current practices of transplantation in these subgroups. In all these subgroups, transplantation reduced long-term mortality by over 50 percent (relative risk, <0.50; $P<0.001$). In all three age groups, the projected increase in the life span after transplantation was greater among patients with diabetes than among those without diabetes.

DISCUSSION

Our findings document that there is substantial selection of healthier patients for placement on the waiting list for transplantation. The magnitude of this bias is similar to that reported previously.[14] The mortality rate for the patients on dialysis who were on the waiting list was about half that of all patients on dialysis when subgroups were analyzed according to age, sex, race, and cause of end-stage renal disease. Thus, studies that compared the outcome among patients who received transplants with that among all patients on dialysis were biased in favor of the former group, because high-risk patients on dialysis who were not candidates for transplantation were included in the reference group. We avoided this selection bias, and we still found large long-term benefits for cadaveric transplantation, despite the increased short-term risk of death after transplantation. Our results also demonstrate that transplantation improved longevity in all groups of recipients, including patients who were 60 to 74 years old at the time of transplantation.

Comparing survival among transplant recipients with that among all patients on dialysis who had been on the waiting list for the same length of time but who had not yet undergone transplantation minimized the time-to-treatment bias. We found that the relative risk of death among recipients of a first cadaveric renal transplant relative to that among patients on the waiting list varies substantially with time. The risk was initially increased. This finding was not unexpected and most likely relates to risks associated with the surgery itself and to the use of high-dose immunosuppressive therapy. The subsequent decrease in the risk of death counterbalanced the initially high rates and resulted in a cumulative survival benefit beginning 244 days after transplantation overall. The long-term reduction in the risk of death was large for all subgroups of patients, averaging 66 percent, as compared with the risk of death among corresponding patients on the waiting list of the same age, sex, and race and with the same cause of end-stage renal disease. Since post-transplantation mortality was assessed independently of allograft function according to an intention-to-treat analysis, this information can be used to advise patients. This approach and methodology have previously been used in a regional registry.[12,14,15] Adjustments for the year of placement on the waiting list and the interval between placement on the list and transplantation minimize the potential effects of an improvement in outcomes over time. Such an improvement has been documented for both patients on dialysis[11,16] and transplant recipients.[11,17]

A major reduction in the relative risk of death does not in itself indicate the extent of the increase in life span. The latter depends on both the death rate and the relative risk. We assessed both clinically relevant measures. The projected increase in life span conferred by transplantation was 10 years overall and ranged from 3 to 17 years according to patient group. The larger estimates need to be viewed with greater caution than the shorter estimates, because the values are extrapolations. Furthermore, both short-term survival and long-term survival have been improving for patients on dialysis and transplant recipients in recent years,[11] and this could also affect the results. In addition, the use of transplants from living donors, which we did not study, should be encouraged, since it has a better outcome than cadaveric transplantation.[18,19]

Our use of the intention-to-treat analysis allows an approximate comparison of transplant recipients with candidates for transplantation who have been on the waiting list for the same length of time. Since patients were enrolled in the study at the time of initial placement on the waiting list, these results can be used to answer questions regarding the risks and benefits of cadaveric renal transplantation as of the time of placement on the list. Assessment of the risks and benefits of transplantation on the day that an organ becomes available would require complete and reliable data on temporary and permanent removal from the waiting list.[20] Removing patients from the analysis at the time of removal from the waiting list would yield a biased result, as is clear from an analysis of the result after the removal of all patients on the waiting list just before death. The latter approach would cause the death rate among patients on the waiting list to be zero, a biased estimate.

Our analysis of U.S. data demonstrates that the patients on dialysis who were placed on the waiting list for transplantation were those with a markedly better likelihood of survival. Recipients of a first cadaveric renal transplant had an initially higher risk of death than those who remained on dialysis but a subsequent long-term benefit. Elderly patients also benefited from transplantation, although the survival benefit was less than that for younger patients.

Supported by a grant from National Institute of Diabetes and Digestive and Kidney Diseases (NO1-DK-3-2202).

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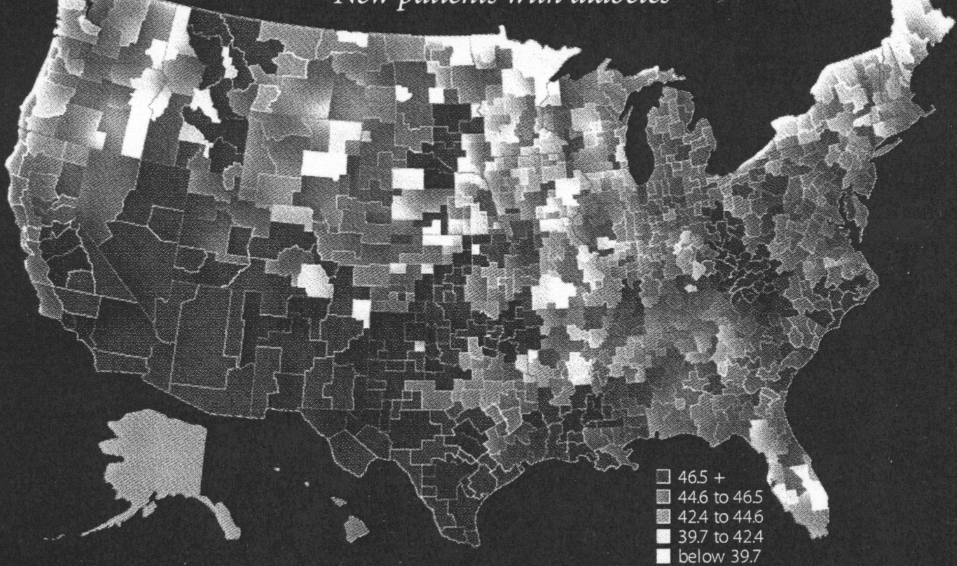
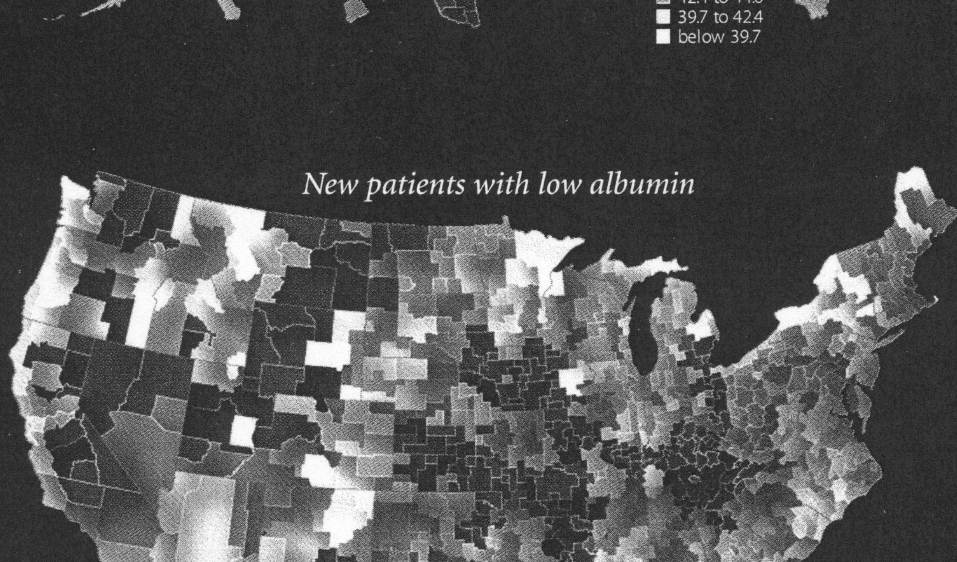
USRDS
United States
Renal Data System

New patients with diabetes



2000 Annual Data Report

New patients with low albumin



Atlas of End-Stage Renal Disease in the United States

Department of Health and Human Services
National Institutes of Health
National Institute of Diabetes and Digestive and Kidney Diseases
Division of Kidney, Urologic, and Hematologic Diseases

EIGHT

Survival, Mortality, & Causes of Death

He was excellent indeed, madam:
the king very lately spoke of him
admiringly and mourningly: he was
skillful enough to have lived still, if
knowledge could be set up against
mortality.

William Shakespeare,
All's Well That Ends Well

All data underlying the figures in this chapter, as well as additional related data, may be viewed & downloaded at www.usrds.org.

Since 1988, first-year death rates for all incident dialysis patients have fallen 38.5%, with the greatest decrease (63.7%) occurring in patients on peritoneal dialysis (fig 8.1). Death rates for transplant patients, consistently much lower than those for patients on dialysis, fell 93% in the same period. Rates have decreased for all age groups of both hemodialysis and peritoneal dialysis patients, with younger patients consistently having lower death rates than their older counterparts. Declines in first-year death rates have been comparable for male and female patients on both modalities—approximately 48% for hemodialysis, and 64% for peritoneal dialysis (figs 8.4–5).

In terms of race, first-year death rates have declined most in Asian patients, 58.3% for hemodialysis and 71.9% for peritoneal dialysis. The rate for white hemodialysis patients shows a slightly higher decline (48%) than that for blacks and Native Americans, 43.1% and 38.8% respectively. This trend is somewhat different for peritoneal patients, however, with the decrease for blacks being 64% compared to 61.7% in whites and 53.9% in Native Americans (figs 8.6–7).

Death rates for diabetics, hypertensive patients, and patients with other renal diseases have begun to converge for hemodialysis patients, but this is not the case for the peritoneal dialysis population, in which diabetics continue to have the highest rates of death (figs 8.8–9). Differences by modality are also apparent in first, second-, and third-to-fifth year death rates (fig 8.10). These patterns suggest that the two dialysis modalities are not proportional to one another over time, a fact that complicates comparisons between them.

Five-year survival curves show that female patients live longer than males across most age groups, races, primary diagnoses, and modalities (figs 8.11–14).

The association over time between death rates and hematocrit levels varies by diabetic status (figs 8.16–18). While the death rates decline with higher hematocrits in both diabetics and nondiabetics, they tend to flatten out as hematocrit levels reach 33%. The consistently lower death rates at higher hematocrit levels support the DOQI target range of 33–36%.

In figures 8.1–15 and 8.19–21 data are adjusted for age, race, gender, and/or diabetic status; they are not, however, adjusted for other clinical factors, such as comorbidity and disease severity, which may influence the death rates. Adjustments for these latter factors, however, are made in figures 8.16–18, which show associations between hematocrit and mortality.

Figures 8.22–32 present death rates for prevalent patient cohorts. Since these cohorts consist of patients with varying amounts of time on ESRD and varying modality histories, and are affected as well by the selection bias related to transplantation, the graphs should be interpreted with caution.

Overall, the fall in death rates has been concurrent with improvements in dialysis therapy and anemia treatment, and with changes in membrane use from cuprophane to synthetic membranes (see Chapter Ten).

Included in this chapter

- Graphs of first-year death rates by modality, age group, gender, race, and primary diagnosis
- Five-year survival curves by gender, age group, race, primary diagnosis, and modality
- Maps of first-, second-, third-, and fourth-year overall death rates, as well as maps of all-cause, infectious, and cardiac death rates
- Graphs of the association between mortality and hematocrit
- Graphs of cause-specific death rates by modality, race, and age group

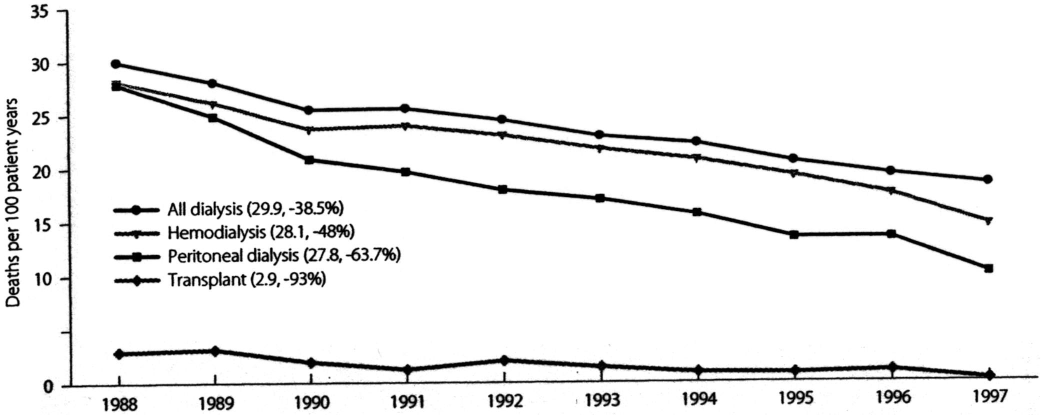


Figure 8.1
First-year death rates by modality
incident patients, adjusted for age, gender, race, & primary diagnosis of diabetes

The number of deaths per 100 patient years in 1988, and the percent change in values between 1988 and 1997, are shown in the legend.

Reference population: the average 1997 incident patient in each modality.

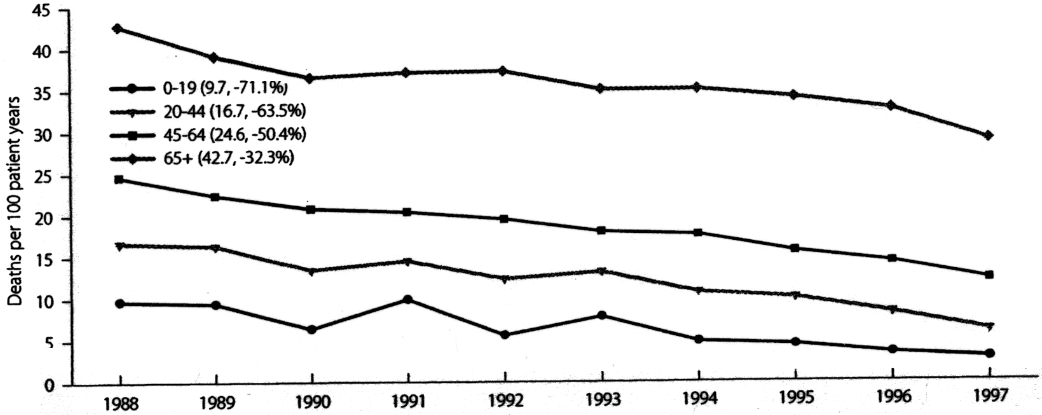


Figure 8.2
First-year death rates by age group
incident hemodialysis patients, adjusted for gender, race, & primary diagnosis of diabetes

The number of deaths per 100 patient years in 1988, and the percent change in values between 1988 and 1997, are shown in the legend.

Reference population: the average 1997 incident hemodialysis patient in each age group.

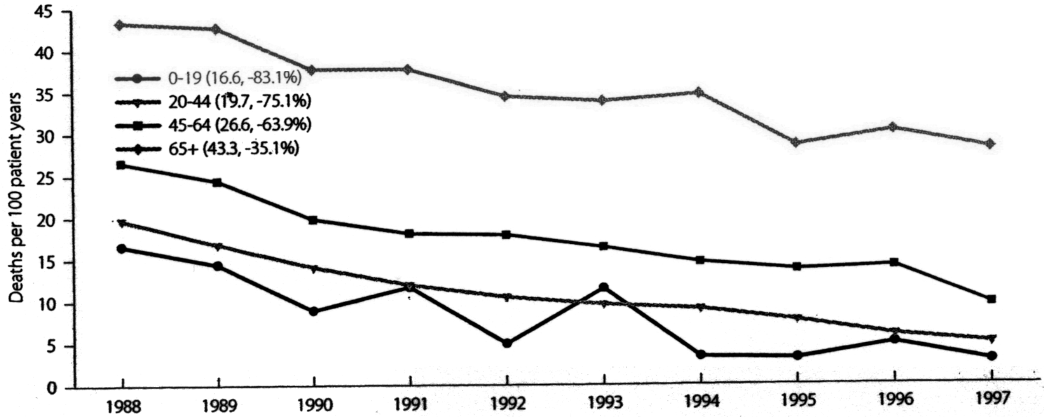


Figure 8.3
First-year death rates by age group
incident peritoneal dialysis patients, adjusted for gender, race, & primary diagnosis of diabetes

The number of deaths per 100 patient years in 1988, and the percent change in values between 1988 and 1997, are shown in the legend.

Reference population: the average 1997 incident peritoneal dialysis patient in each age group.

Figure 8.4
First-year death rates by gender
incident hemodialysis patients, adjusted for age, race, & primary diagnosis of diabetes

The number of deaths per 100 patient years in 1988, and the percent change in values between 1988 and 1997, are shown in the legend.

Reference population: the average 1997 incident hemodialysis patient of each gender.

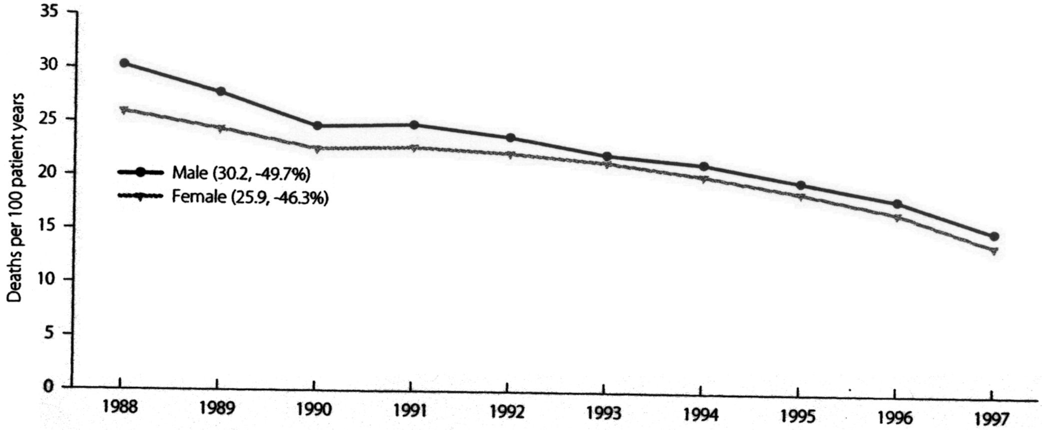


Figure 8.5
First-year death rates by gender
incident peritoneal dialysis patients, adjusted for age, race, & primary diagnosis of diabetes

The number of deaths per 100 patient years in 1988, and the percent change in values between 1988 and 1997, are shown in the legend.

Reference population: the average 1997 incident peritoneal dialysis patient of each gender.

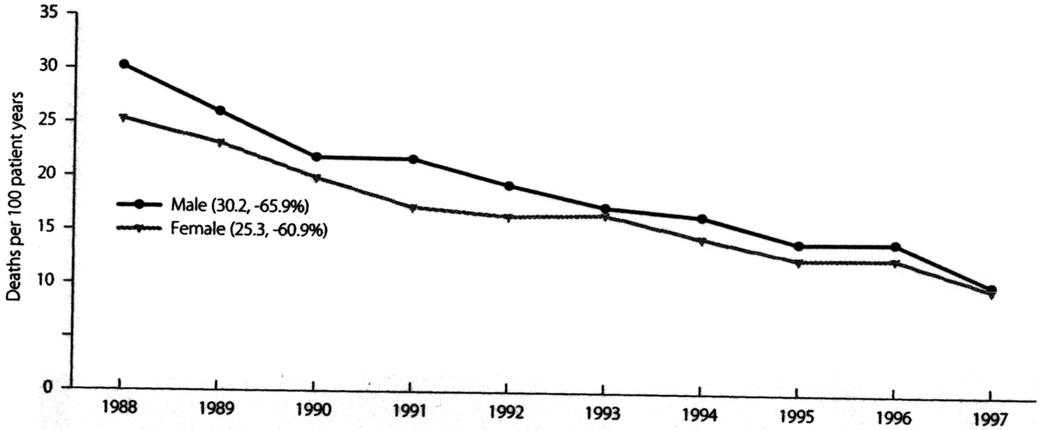
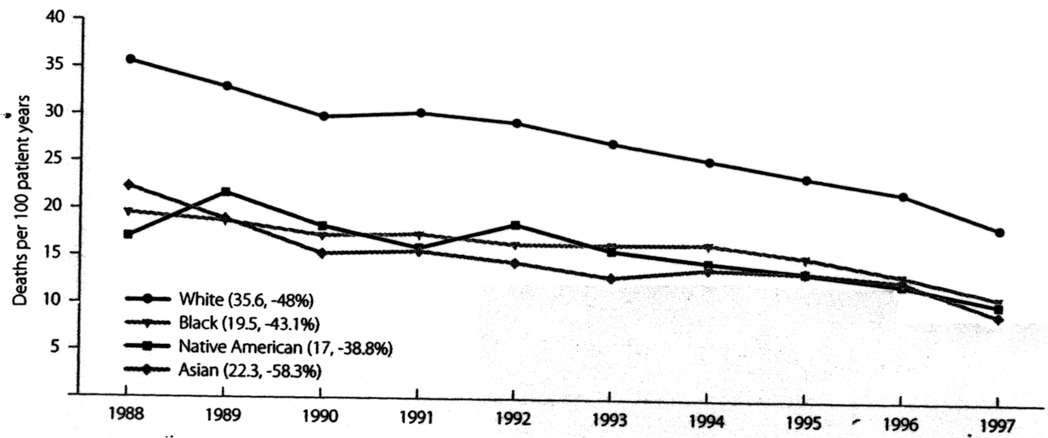


Figure 8.6
First-year death rates by race
incident hemodialysis patients, adjusted for age, gender, & primary diagnosis of diabetes

The number of deaths per 100 patient years in 1988, and the percent change in values between 1988 and 1997, are shown in the legend.

Reference population: the average 1997 incident hemodialysis patient of each race.



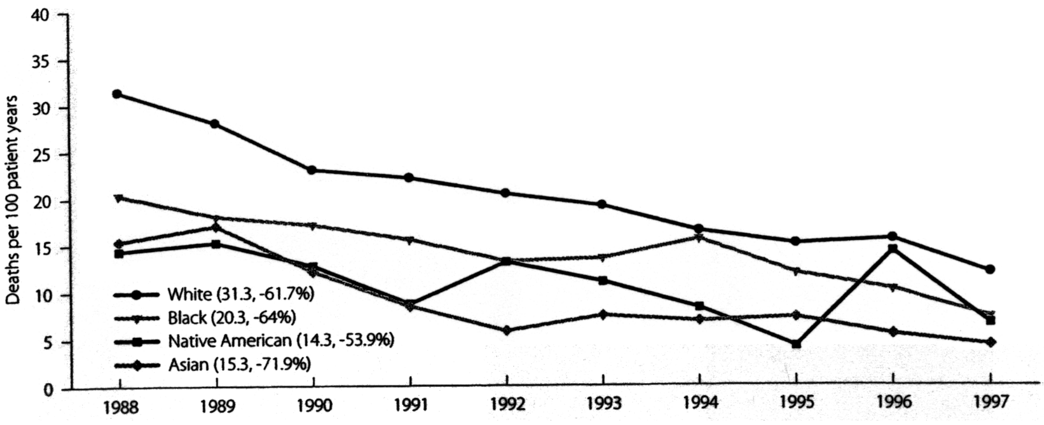


Figure 8.7
First-year death rates by race
incident peritoneal dialysis patients, adjusted for age, gender, & primary diagnosis of diabetes

The number of deaths per 100 patient years in 1988, and the percent change in values between 1988 and 1997, are shown in the legend.

Reference population: the average 1997 incident peritoneal dialysis patient of each race.

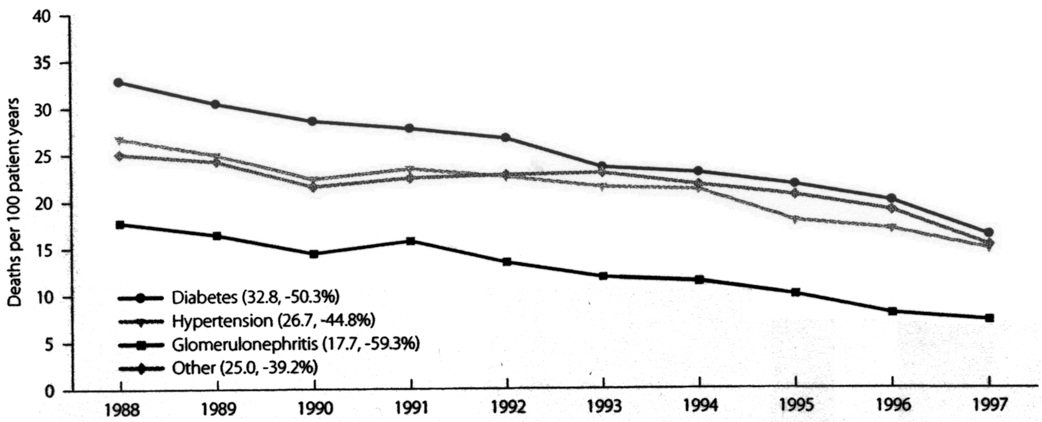


Figure 8.8
First-year death rates by primary diagnosis
incident hemodialysis patients, adjusted for age, gender, & race

The number of deaths per 100 patient years in 1988, and the percent change in values between 1988 and 1997, are shown in the legend.

Reference population: the average 1997 incident hemodialysis patient with each primary diagnosis.

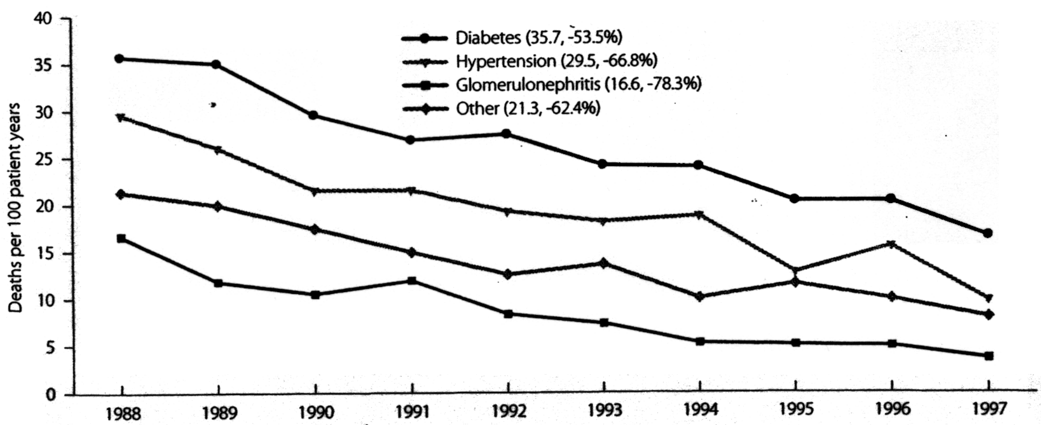


Figure 8.9
First-year death rates by primary diagnosis
incident peritoneal dialysis patients, adjusted for age, gender, & race

The number of deaths per 100 patient years in 1988, and the percent change in values between 1988 and 1997, are shown in the legend.

Reference population: the average 1997 incident peritoneal dialysis patient with each primary diagnosis.

Figure 8.10
First-, second-, & third-to-fifth year annual death rates
incident patients, adjusted for age, gender, race, & primary diagnosis of diabetes

The number of deaths per 100 patient years in 1988, and the percent change in values between 1988 and the last year shown for each death rate, are shown in the legends.

Reference population: the average 1997 incident patient on each modality.

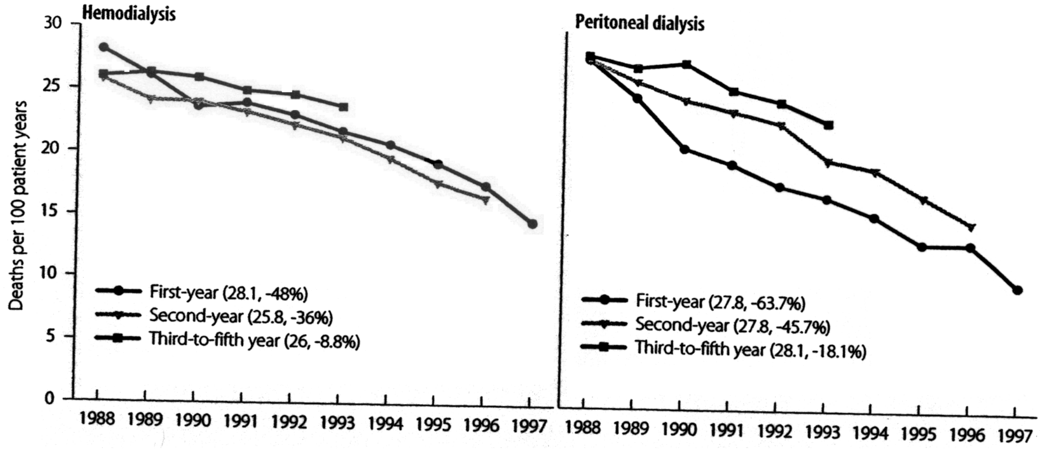


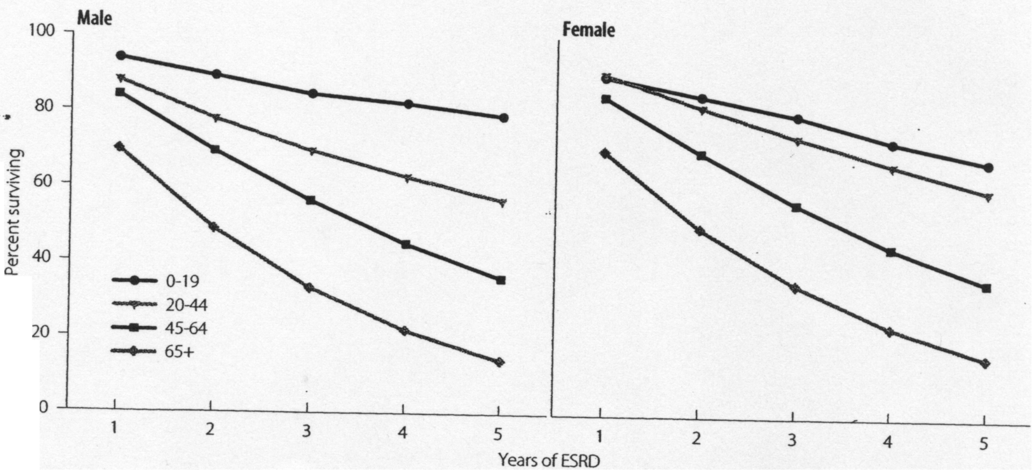
Table 8.1
Expected remaining lifetimes (years) by race & gender
prevalent patients, 1998

Reference: Table H.3, H.4, H.12, and H.13.

	Dialysis								Transplant							
	White		Black		Nat. American		Asian		White		Black		Nat. American		Asian	
Age	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
0-14	19.5	18.7	23.1	22.2	26.0	27.1	30.4	30.9	47.5	47.4	45.9	44.2	52.3	50.1	52.3	54.5
15-19	16.4	15.8	20.8	19.9	20.6	21.2	24.1	24.4	35.4	35.6	35.1	34.0	39.1	37.3	39.4	41.5
20-24	13.6	13.0	17.6	16.8	17.3	17.9	20.5	20.9	31.9	32.3	31.6	30.9	34.9	33.3	35.2	37.3
25-29	11.5	11.0	15.1	14.4	14.7	15.3	17.6	18.0	27.6	28.1	27.4	26.8	30.3	28.9	30.6	32.7
30-34	9.7	9.3	12.9	12.3	12.4	13.0	15.0	15.4	23.7	24.4	23.6	23.1	26.0	24.8	26.4	28.3
35-39	8.3	8.1	11.1	10.7	10.6	11.3	12.9	13.3	20.1	20.9	20.0	19.7	21.9	20.9	22.3	24.1
40-44	7.2	7.1	9.6	9.3	9.1	9.7	11.0	11.5	16.7	17.4	16.4	16.4	18.0	17.2	18.3	20.0
45-49	6.2	6.3	8.3	8.0	7.7	8.3	9.3	9.8	13.7	14.3	13.4	13.4	14.4	13.9	14.8	16.1
50-54	5.3	5.2	7.0	6.8	6.5	7.0	7.7	8.2	10.7	11.1	10.4	10.5	11.0	10.7	11.3	12.3
55-59	4.5	4.6	5.9	5.9	5.4	6.0	6.6	7.0	7.7	8.0	7.5	7.6	7.8	7.6	7.9	8.6
60-64	3.7	3.9	5.0	5.0	4.5	4.9	5.4	5.7	4.2	4.4	4.2	4.3	4.3	4.2	4.3	4.6
65-69	3.0	3.2	4.0	4.1	3.6	4.0	4.3	4.6								
70-74	2.7	2.7	3.4	3.5	3.0	3.4	3.6	3.9								
75-79	2.3	2.4	2.9	2.9	2.5	2.8	2.9	3.2								
80-84	2.0	2.0	2.4	2.4	2.0	2.4	2.4	2.7								
85 +	1.6	1.6	1.9	1.9	1.6	1.9	1.9	2.1								

Figure 8.11
Five-year survival curves by age group & gender
incident dialysis patients, 1993, adjusted for race & primary diagnosis of diabetes

Reference population: the average 1997 incident dialysis patient of the same gender and age group.



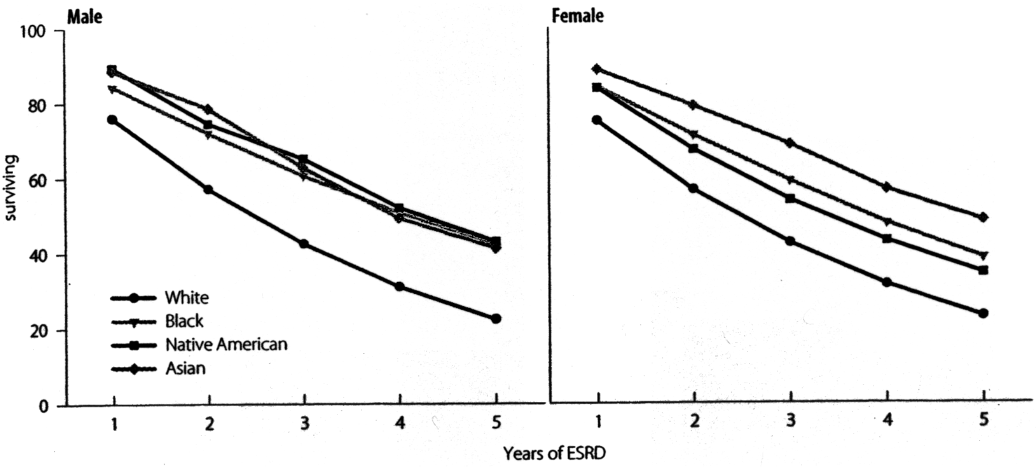


Figure 8.12
Five-year survival by race & gender
incident dialysis patients, 1993, adjusted for age & primary diagnosis of diabetes

Reference population: the average 1997 incident dialysis patient of the same gender and race.

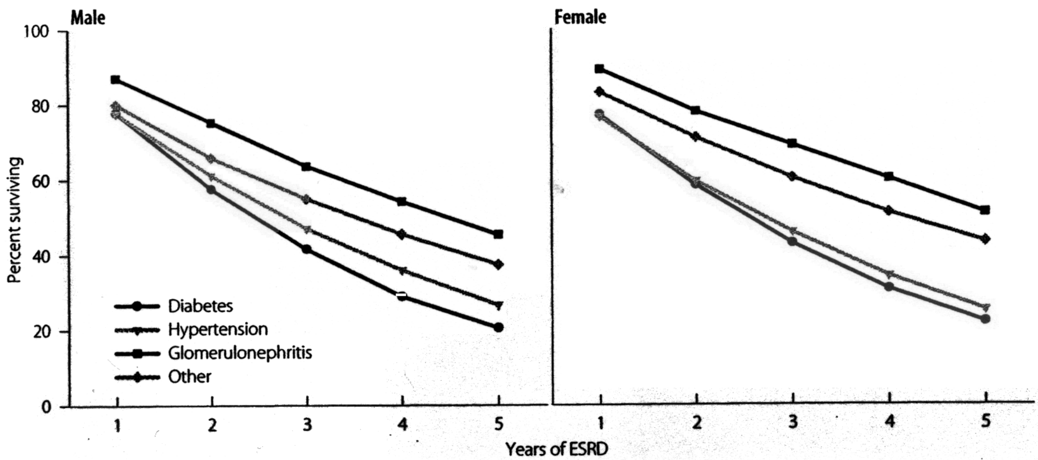


Figure 8.13
Five-year survival by primary diagnosis & gender
incident dialysis patients, 1993, adjusted for age & race

Reference population: the average 1997 incident dialysis patient of the same gender and primary diagnosis.

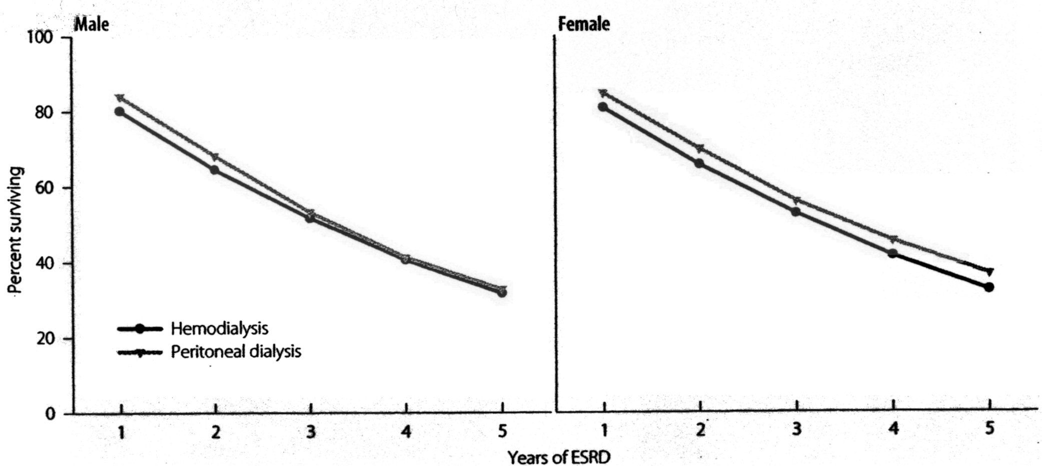
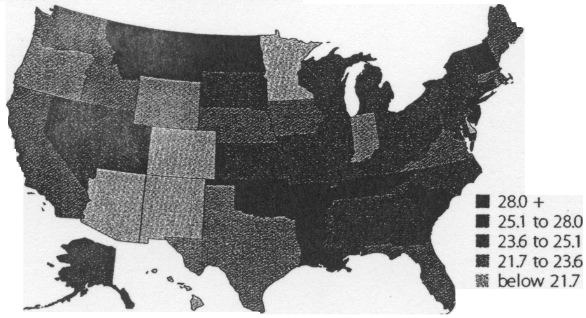


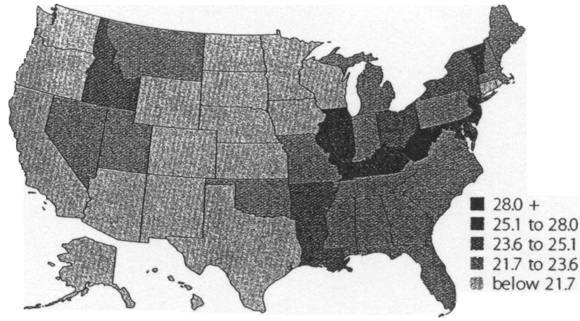
Figure 8.14
Five-year survival by modality & gender
incident dialysis patients, 1993, adjusted for age, race, & primary diagnosis of diabetes

Reference population: the average 1997 incident dialysis patient of the same gender and modality.

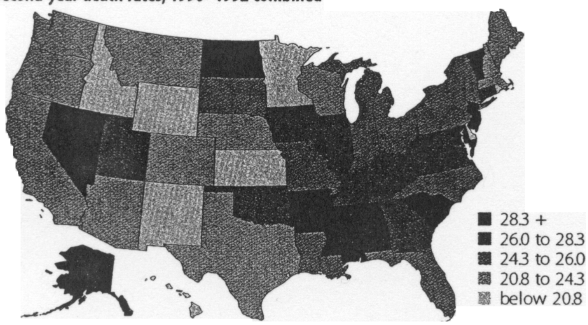
First-year death rates, 1990–1992 combined



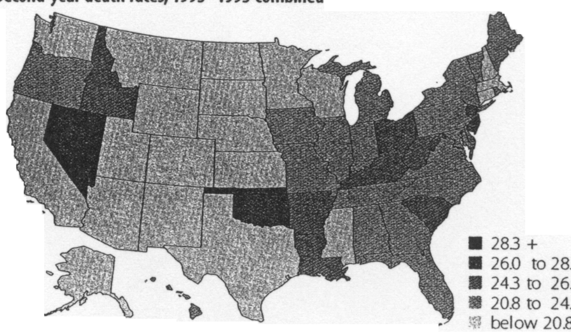
First-year death rates, 1993–1995 combined



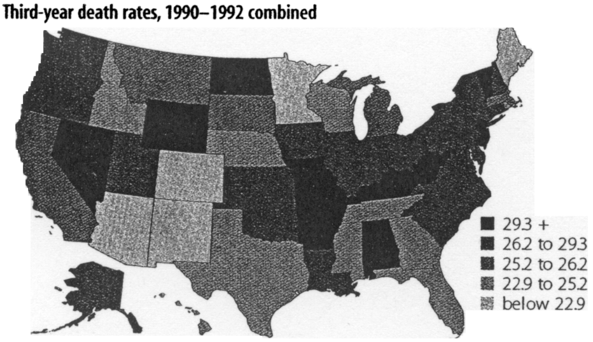
Second-year death rates, 1990–1992 combined



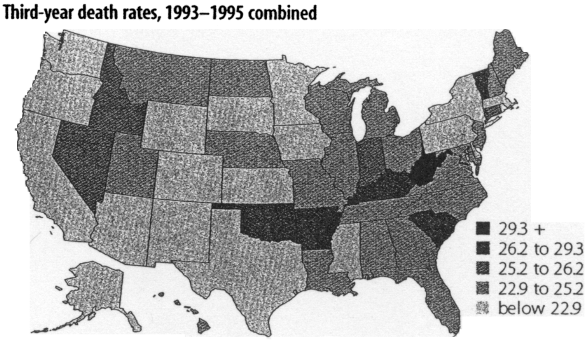
Second-year death rates, 1993–1995 combined



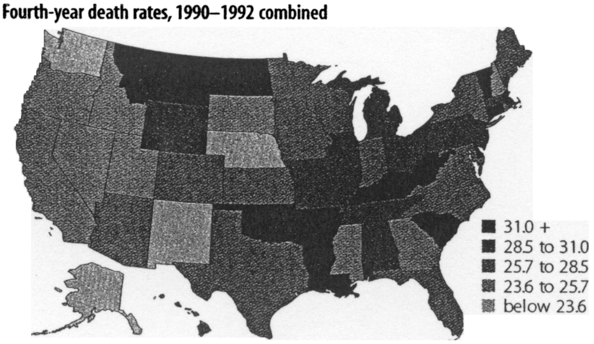
Third-year death rates, 1990–1992 combined



Third-year death rates, 1993–1995 combined



Fourth-year death rates, 1990–1992 combined



Fourth-year death rates, 1993–1995 combined

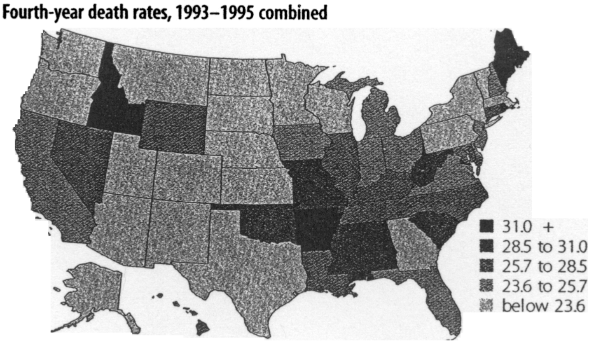


Figure 8.15

First-, second-, third-, & fourth-year death rates

per 100 patient years at risk, incident dialysis patients, by state, adjusted for age, gender, race, & primary diagnosis of diabetes

Reference population: the average 1997 incident dialysis patient.

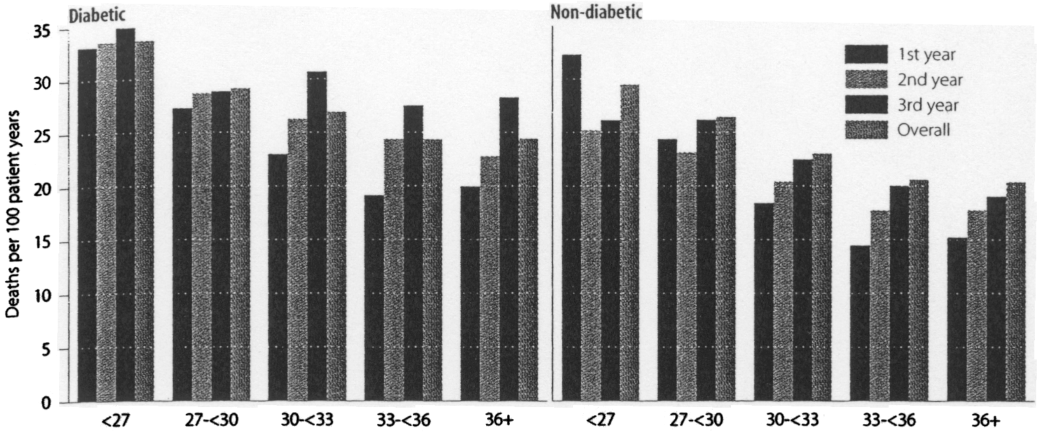


Figure 8.16
Associations between mortality & hematocrit level by years of follow-up
incident dialysis patients, 1993–1996 combined, adjusted for patient characteristics, comorbidity, & severity of disease in the entry period

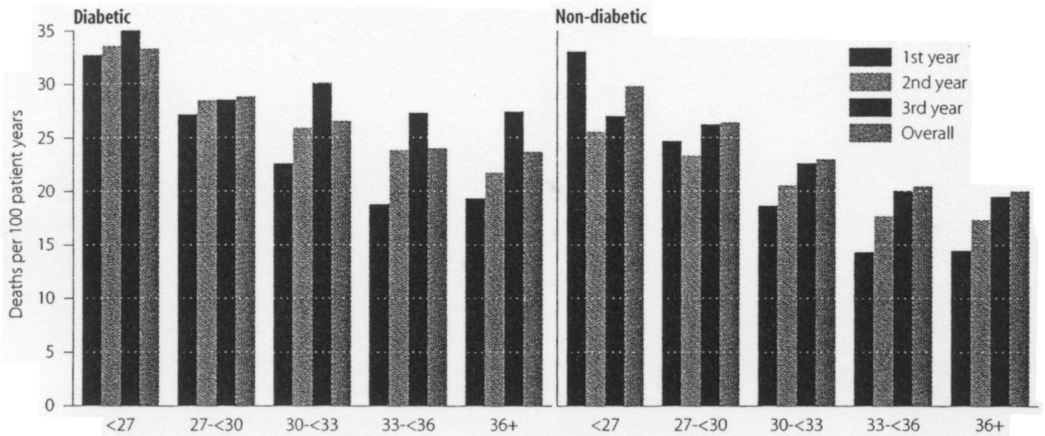


Figure 8.17
Associations between mortality & hematocrit level by years of follow-up
incident hemodialysis patients, 1993–1996 combined, adjusted for patient characteristics, comorbidity, & severity of disease in the entry period

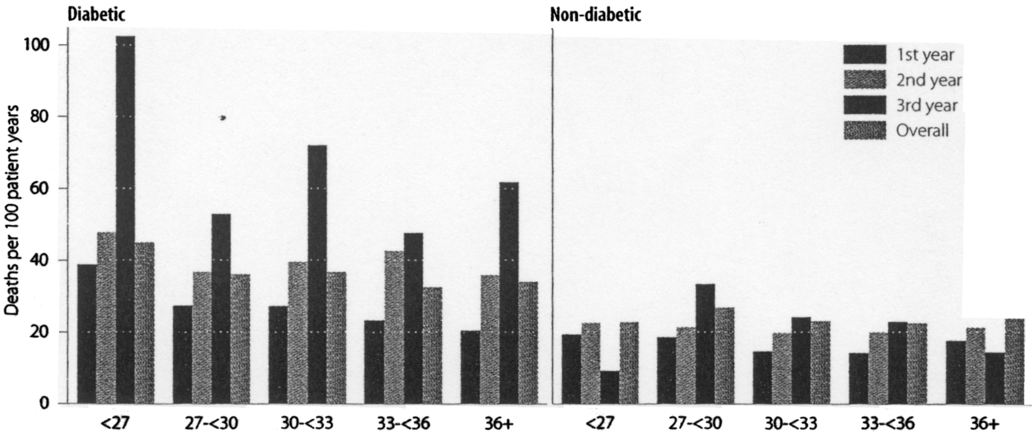
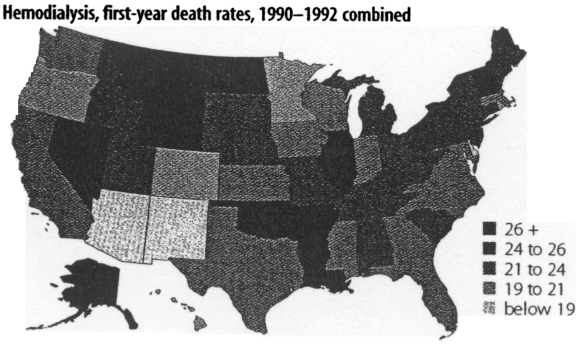
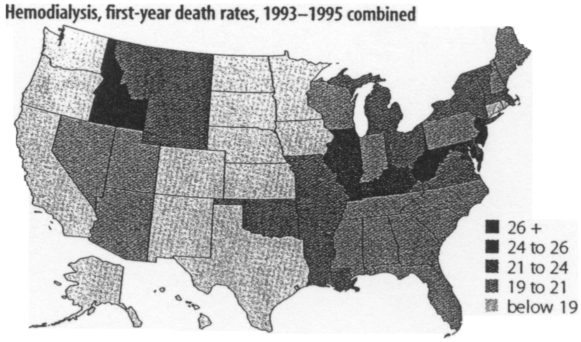


Figure 8.18
Associations between mortality & hematocrit level by years of follow-up
incident peritoneal dialysis patients, 1993–1996 combined, adjusted for patient characteristics, comorbidity, & severity of disease in the entry period

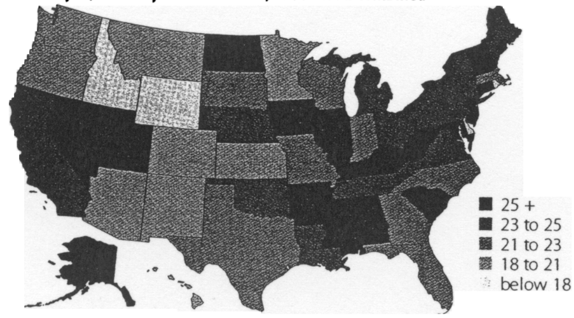
Hemodialysis, first-year death rates, 1990–1992 combined



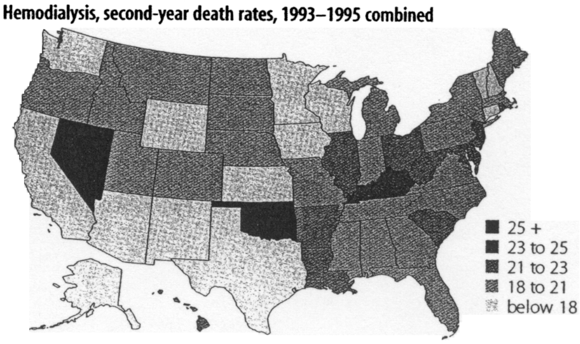
Hemodialysis, first-year death rates, 1993–1995 combined



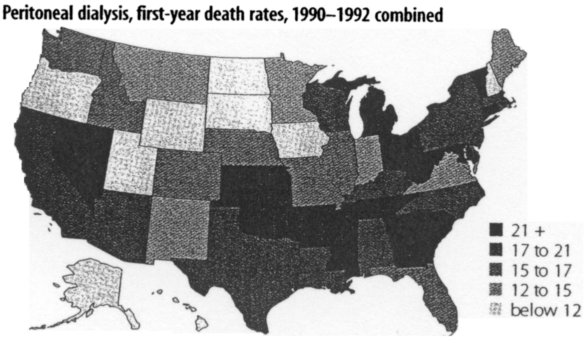
Hemodialysis, second-year death rates, 1990–1992 combined



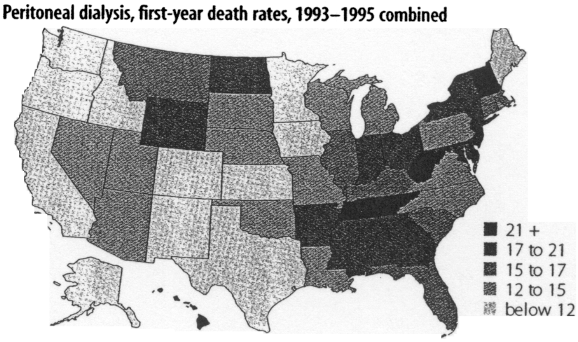
Hemodialysis, second-year death rates, 1993–1995 combined



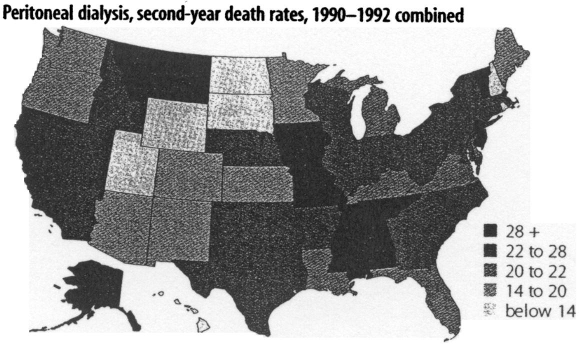
Peritoneal dialysis, first-year death rates, 1990–1992 combined



Peritoneal dialysis, first-year death rates, 1993–1995 combined



Peritoneal dialysis, second-year death rates, 1990–1992 combined



Peritoneal dialysis, second-year death rates, 1993–1995 combined

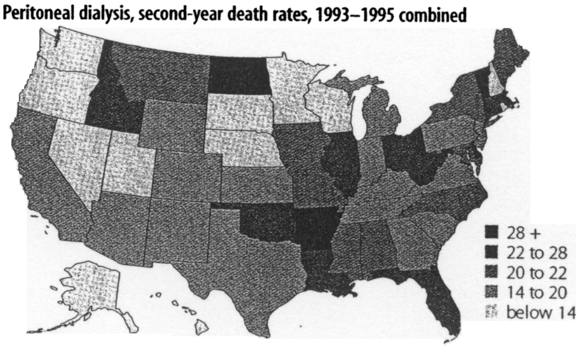


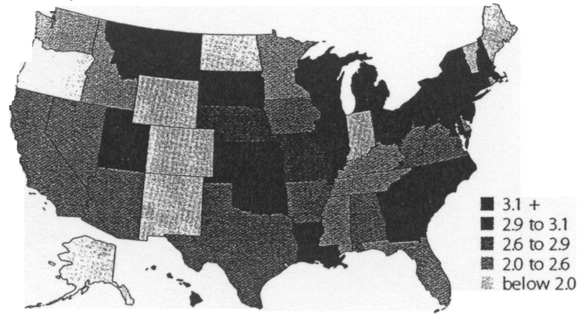
Figure 8.19

All-cause death rates

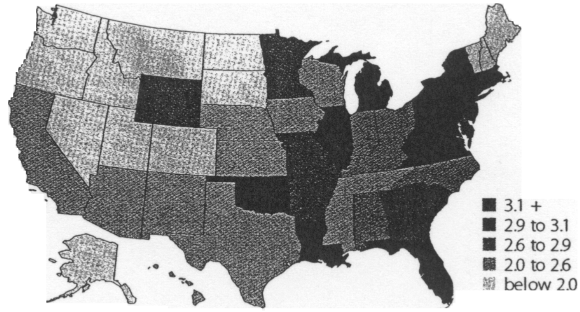
per 100 patient years at risk, incident patients, by state, adjusted for age, gender, race, & diabetic status

While all-cause death rates have clearly decreased since 1992, an analysis that includes more detailed adjustments is required to understand the geographic patterns. Death rates are influenced not only by age, gender, race, and diabetic status, but by dialysis therapy, hematocrit level, membrane use, transplant rates, and modality change rates. The complexity of comparing hemodialysis and peritoneal dialysis, particularly over varying lengths of follow-up time, should also be considered. Reference population: the average 1997 incident patient of the same modality.

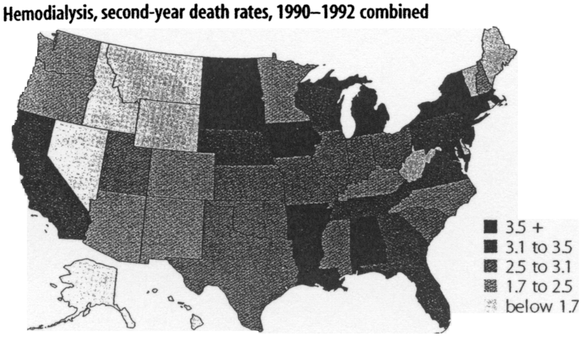
Hemodialysis, first-year death rates, 1990–1992 combined



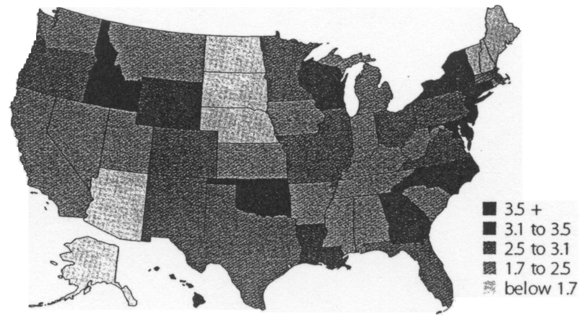
Hemodialysis, first-year death rates, 1993–1995 combined



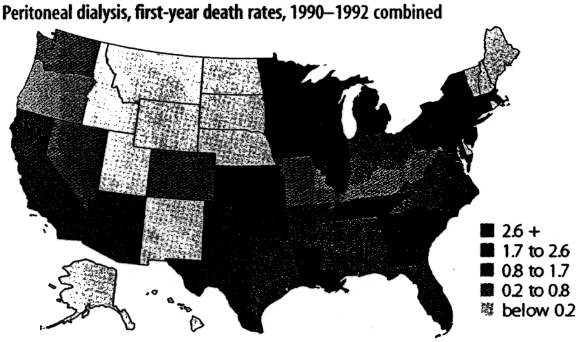
Hemodialysis, second-year death rates, 1990–1992 combined



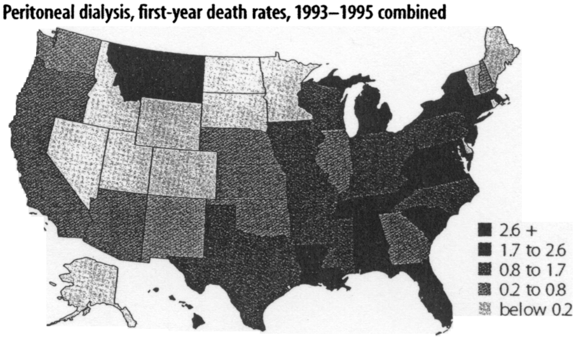
Hemodialysis, second-year death rates, 1993–1995 combined



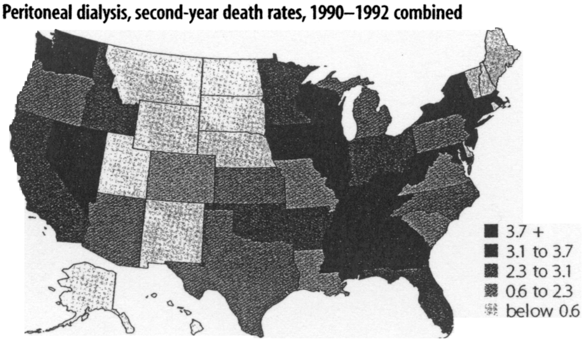
Peritoneal dialysis, first-year death rates, 1990–1992 combined



Peritoneal dialysis, first-year death rates, 1993–1995 combined



Peritoneal dialysis, second-year death rates, 1990–1992 combined



Peritoneal dialysis, second-year death rates, 1993–1995 combined

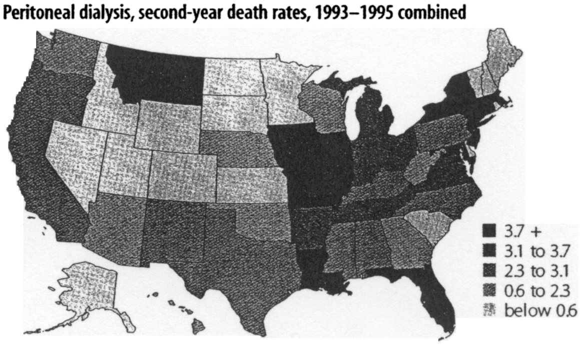


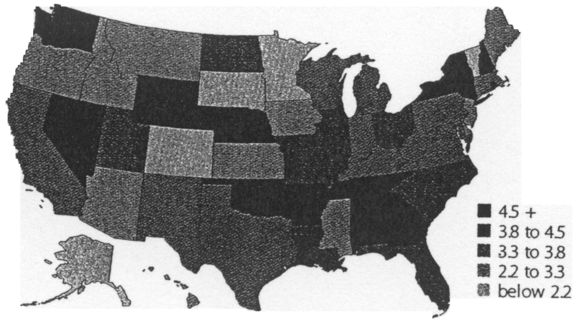
Figure 8.20

Infectious death rates

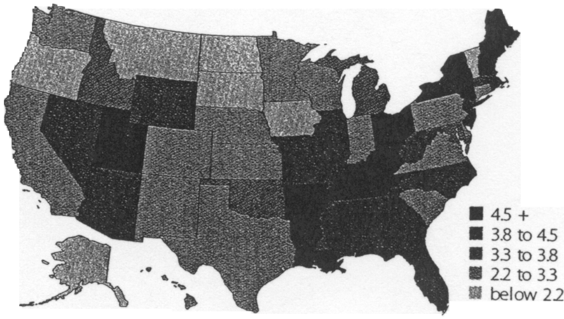
per 100 patient years at risk, incident patients, by state, adjusted for age, gender, race, & diabetic status

The distribution of infectious death rates parallels the pattern of insertion rates for central venous catheters (fig 4.15). Rates of peritonitis and catheter complications should be investigated for their possible contribution to the geographic variation in infectious death rates, as should the effect of recently improved peritoneal dialysis delivery systems (which reduce the risk of contamination) and the differences between CAPD and CCPD. Reference population: the average 1997 incident patient of the same modality.

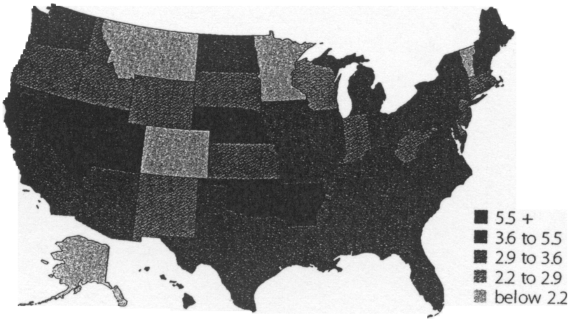
Hemodialysis, first-year death rates, 1990–1992 combined



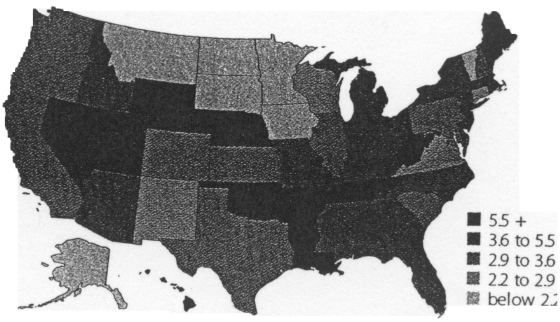
Hemodialysis, first-year death rates, 1993–1995 combined



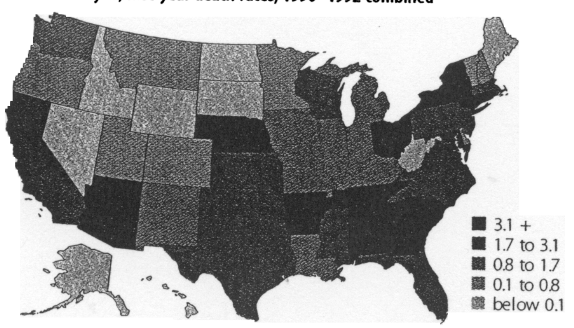
Hemodialysis, second-year death rates, 1990–1992 combined



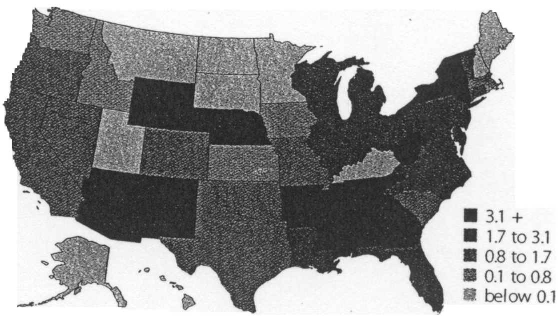
Hemodialysis, second-year death rates, 1993–1995 combined



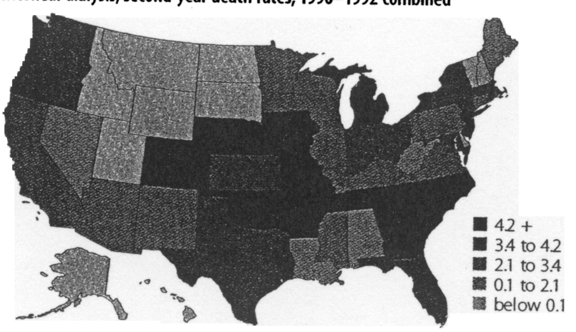
Peritoneal dialysis, first-year death rates, 1990–1992 combined



Peritoneal dialysis, first-year death rates, 1993–1995 combined



Peritoneal dialysis, second-year death rates, 1990–1992 combined



Peritoneal dialysis, second-year death rates, 1993–1995 combined

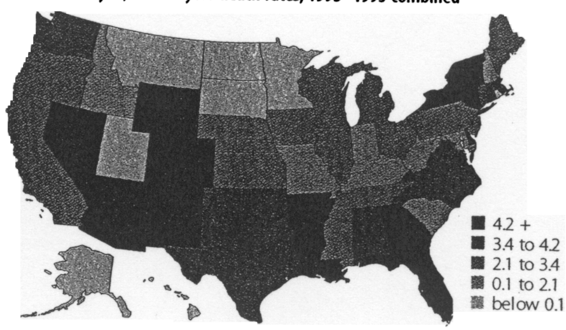


Figure 8.21

Cardiac death rates

per 100 patient years at risk, incident patients, by state, adjusted for age, gender, race, & diabetic status

More detailed analyses of regional differences in cardiac death rates should evaluate the influences of comorbidity, disease severity, transplantation rates, cardiovascular intervention, and monitoring of diabetic patients for glycemic control and lipid disorders. Reference population: the average 1997 incident patient of the same modality.

Table 8.2
Cause of death categories
from HCFA Death Notification Form 2746

Acute myocardial infarction

Cardiac arrest, cause unknown

Cardiac, other
- Atherosclerotic heart disease
- Cardiac arrhythmia
- Cardiomyopathy
- Pericarditis, including cardiac tamponade
- Pulmonary edema due to exogenous fluid
- Valvular heart disease

Cerebrovascular (CVD, CVA/TIA)
- Cerebrovascular accident
- Ischemic brain damage

Infection
- AIDS
- Fungal peritonitis
- Hepatitis B
- Infection, other
- Other viral hepatitis
- Pulmonary infection, bacterial
- Pulmonary infection, fungal
- Pulmonary infection, other
- Septicemia, peritonitis
- Septicemia, PVD/gangrene
- Septicemia, vascular access
- Septicemia, other
- Tuberculosis
- Viral infection, CMV
- Viral infection, other

Malignancy
- Malignant disease, history of immunosuppressive treatment
- Malignant disease, other

Other known causes
- Accident related to treatment
- Accident unrelated to treatment
- Air embolism
- Bone marrow depression
- Cachexia
- Chronic obstr. pulmonary disease
- Cirrhosis
- Complications of surgery
- Dementia
- Diabetic coma, hypo/hyperglycemia
- Drug overdose
- Drug overdose, street drugs
- GI hemorrhage
- Hemorrhage, dialysis circuit
- Hemorrhage, ruptured vascular access
- Hemorrhage, surgery
- Hemorrhage, transplant site
- Hemorrhage, vascular access
- Hyperkalemia
- Liver failure, cause unknown
- Liver-drug toxicity
- Mesenteric infarction/ischemic bowel
- Other hemorrhage
- Other identified cause
- Pancreatitis
- Perforation of bowel
- Perforation of peptic ulcer
- Polycystic liver disease
- Pulmonary embolus
- Seizures
- Suicide

Unknown
- Includes causes of death not recorded or no Death Notification form

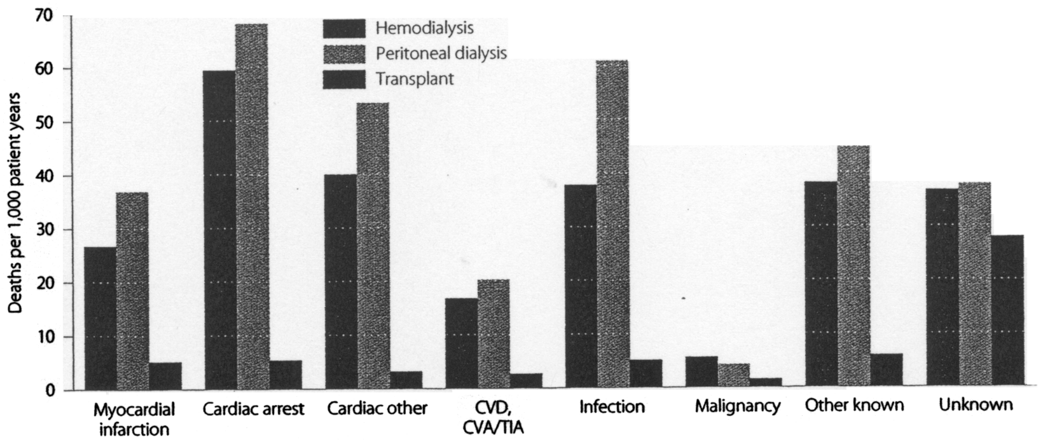


Figure 8.22
Cause-specific death rates by modality
prevalent diabetic patients aged 20 & older, 1996–1998 combined, unadjusted

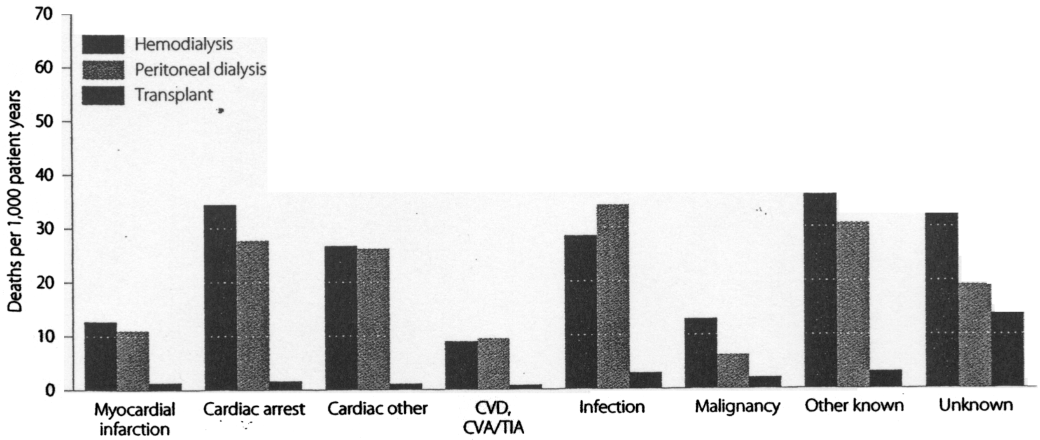


Figure 8.23
Cause-specific death rates by modality
prevalent non-diabetic patients aged 20 & older, 1996–1998 combined, unadjusted

Comparisons of prevalent death rates across modalities should be made with caution, as the rates may be influenced by patient time on ESRD, transplant rates, comorbidity, disease severity, dialysis therapy, and hematocrit level.

Figure 8.24
Cause-specific death rates by race
prevalent male hemodialysis patients aged 20 & older, 1996–1998 combined, unadjusted

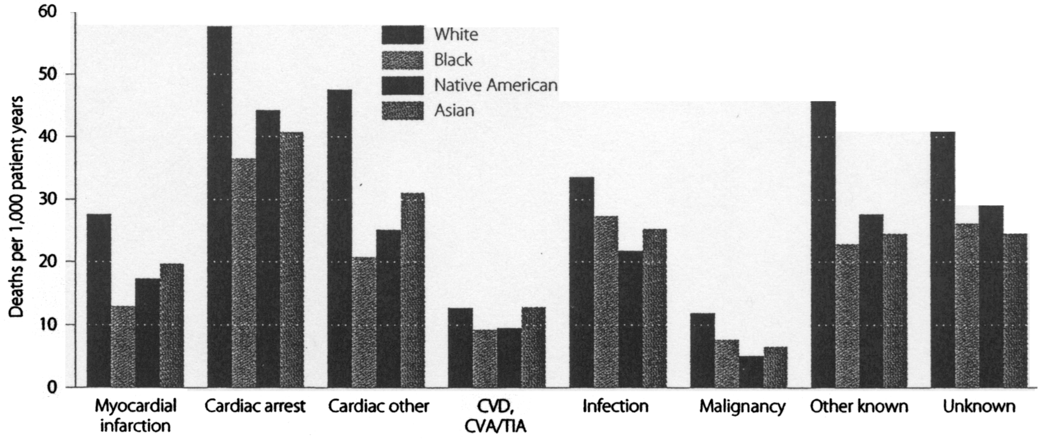


Figure 8.25
Cause-specific death rates by race
prevalent female hemodialysis patients aged 20 & older, 1996–1998 combined, unadjusted

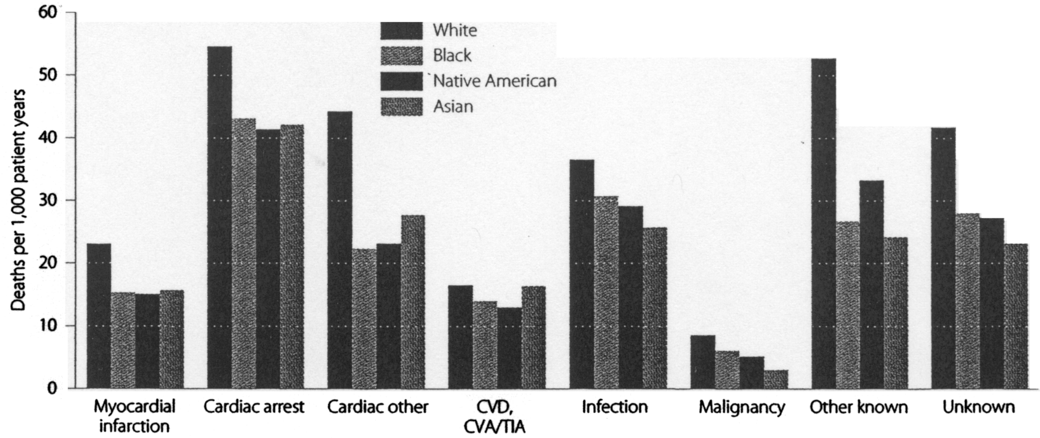


Figure 8.26
Cause-specific death rates by race
prevalent male peritoneal dialysis patients aged 20 & older, 1996–1998 combined, unadjusted

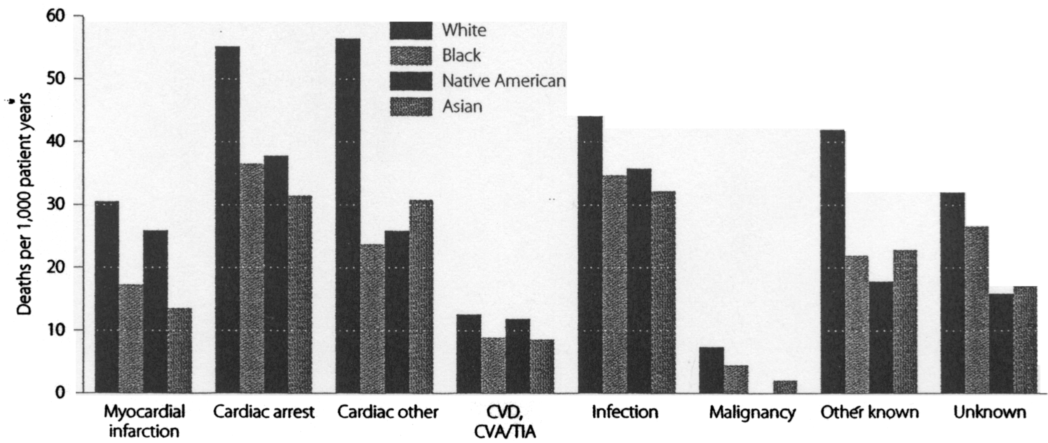


Figure 8.27
Cause-specific death rates by race
prevalent female peritoneal dialysis patients aged 20 & older, 1996–1998 combined, unadjusted

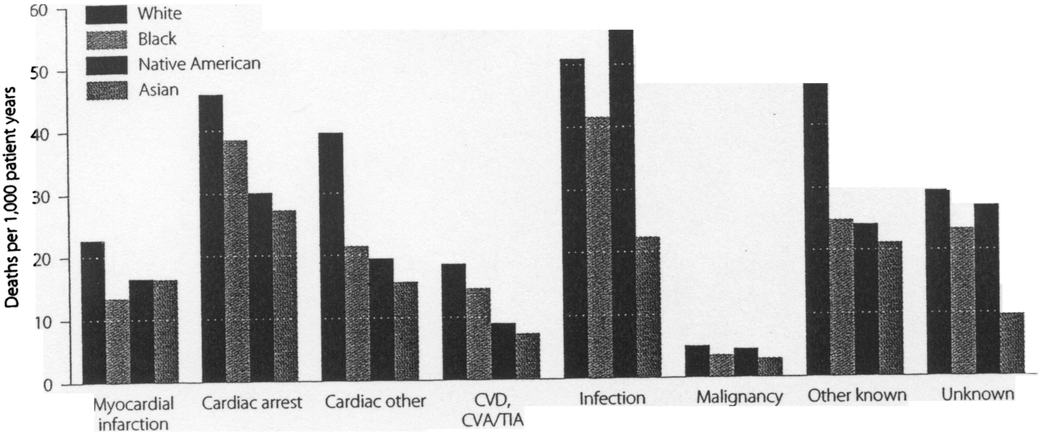


Figure 8.28
Cause-specific death rates by race
prevalent male transplant patients aged 20 & older, 1996–1998 combined, unadjusted

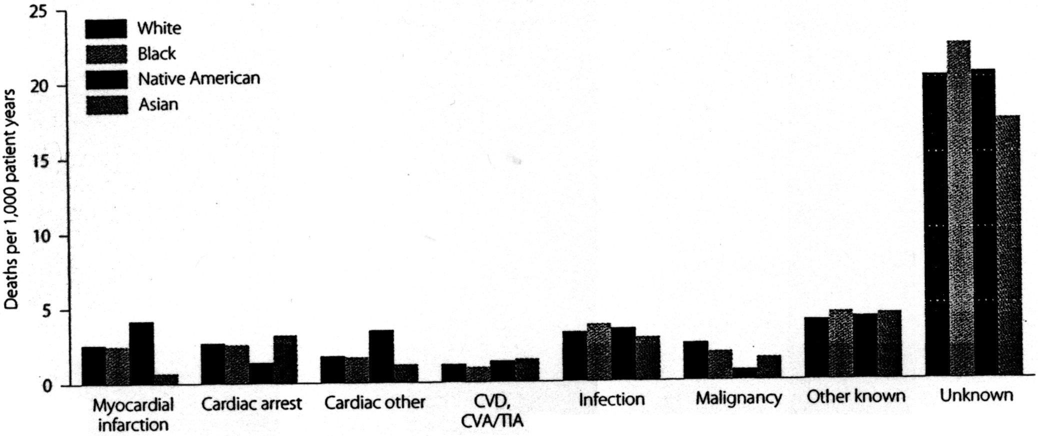


Figure 8.29
Cause-specific death rates by race
prevalent female transplant patients aged 20 & older, 1996–1998 combined, unadjusted

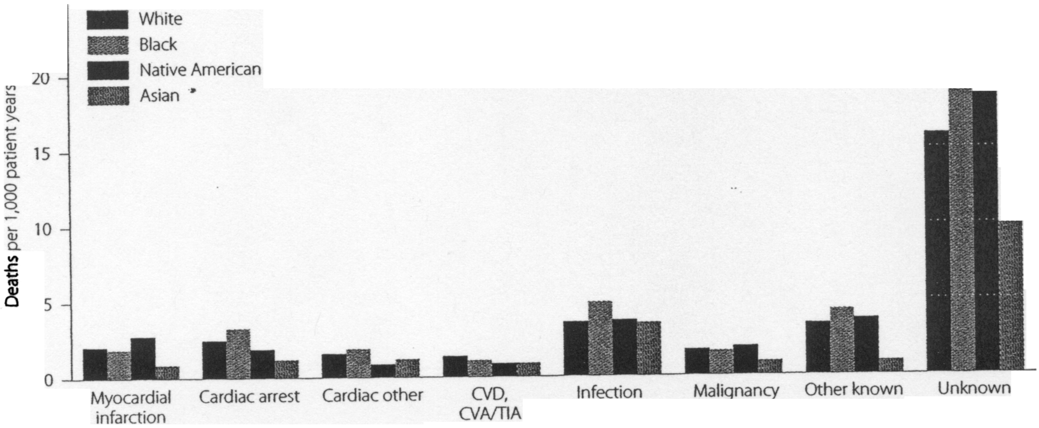


Figure 8.30
Cause-specific death rates by age group
prevalent hemodialysis patients, 1996–1998 combined, unadjusted

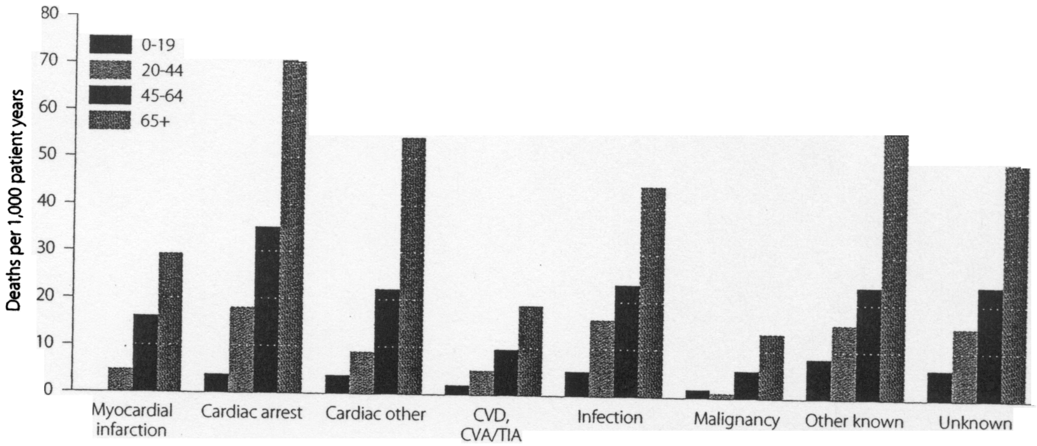


Figure 8.31
Cause-specific death rates by age group
prevalent peritoneal dialysis patients, 1996–1998 combined, unadjusted

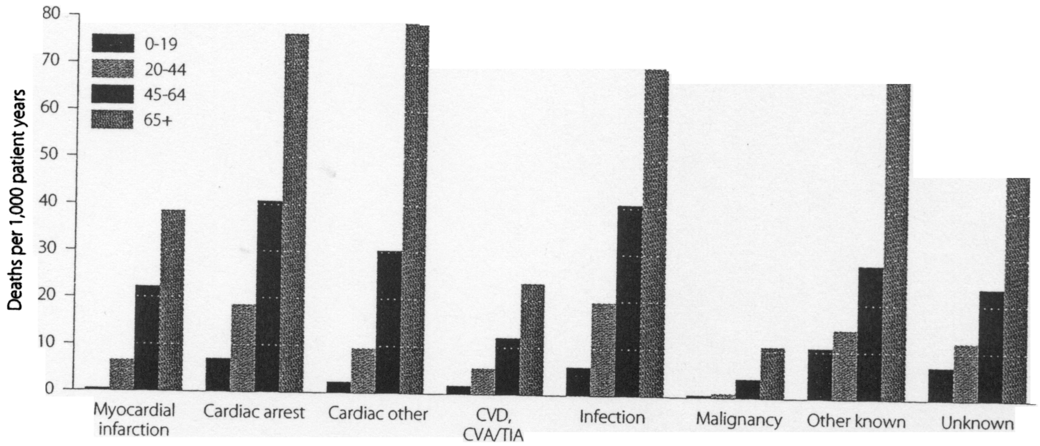
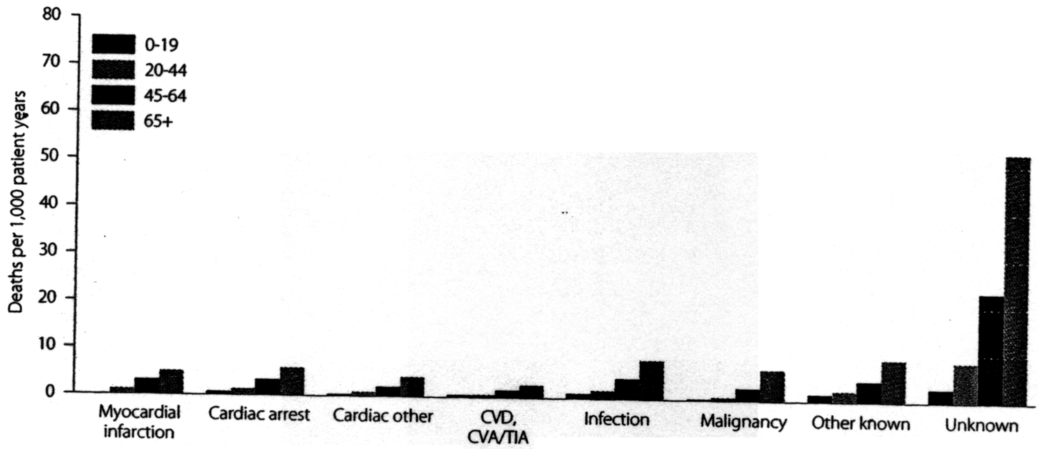


Figure 8.32
Cause-specific death rates by age group
prevalent transplant patients, 1996–1998 combined, unadjusted



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Computer simulations of peritoneal fluid transport in CAPD

BENGT RIPPE, GUNNAR STELIN, and BÖRJE HARALDSSON

Department of Nephrology, University Hospital of Lund, Lund; Department of Nephrology, Sahlgrenska Hospital, Göteborg; and Department of Physiology, University of Göteborg, Göteborg, Sweden

Computer simulations of peritoneal fluid transport in CAPD. To model the changes in intraperitoneal dialysate volume (IPV) occurring over dwell time under various conditions in continuous ambulatory peritoneal dialysis (CAPD), we have, using a personal computer (PC), numerically integrated the phenomenological equations that describe the net ultrafiltration (UF) flow existing across the peritoneal membrane in every moment of a dwell. Computer modelling was performed according to a three-pore model of membrane selectivity as based on current concepts in capillary physiology. This model comprises small "paracellular" pores (radius ≈ 47 Å) and "large" pores (radius ≈ 250 Å), together accounting for ≈98% of the total UF-coefficient (L_pS), and also "transcellular" pores (pore radius ≈4 to 5 Å) accounting for 1.5% of L_pS. Simulated curves made a good fit to IPV versus time data obtained experimentally in adult patients, using either 1.36 or 3.86% glucose dialysis solutions, under control conditions; when the peritoneal UF-coefficient was set to 0.082 ml/min/mm Hg, the glucose reflection coefficient was 0.043 and the peritoneal lymph flow was set to 0.3 ml/min. Also, theoretical predictions regarding the IPV versus time curves agreed well with the computer simulated results for perturbed values of effective peritoneal surface area, L_pS, glucose permeability-surface area product (PS or "MTAC"), intraperitoneal dialysate volume and dialysate glucose concentration. Thus, increasing the peritoneal surface area caused the IPV versus time curves to peak earlier than during control, while the maximal volume ultrafiltered was not markedly affected. However, increasing the glucose PS caused both a reduction in the IPV versus time curve "peak time" and in the "peak height" of the curves. The latter pattern was also seen when the dialysate volume was reduced. It is suggested that computer modelling based on a three-pore model of membrane selectivity may be a useful tool for describing the IPV versus time relationships under various conditions in CAPD.

The exchange characteristics of the peritoneal membrane vary greatly among individual patients on continuous ambulatory peritoneal dialysis (CAPD) [1, 2]. After years of PD treatment many patients develop an increased peritoneal glucose clearance, which will reduce their capacity of removing fluid by ultrafiltration (osmosis), on ordinary dialysis prescriptions [3–7]. To manage these patients it is essential to have knowledge of the factors that determine the exchange of fluid across the peritoneal membrane, and hence, the variation in intraperitoneal dialysate volume (IPV) over cycle time.

In a previous study we have discussed the principal phenomenological membrane coefficients necessary to describe the IPV versus time relationships under ordinary conditions [8]. The major factors affecting the IPV versus time curves are: the peritoneal osmotic conductance to glucose, that is, the product of the peritoneal UF-coefficient (L_pS) and the glucose osmotic reflection coefficient (σ_g)[1], the glucose permeability surface area product (PS_g), the peritoneal lymph flow (L), and finally, the intraperitoneal glucose concentration and dialysate volume at the start of each cycle, respectively [8–11].

From the phenomenological equations described previously [8] it is possible to predict in approximate terms how the IPV versus time curve during a single dwell will vary in response to variation in the factors mentioned above. In the present paper we deal with the issue more pragmatically, using a personal computer (PC) to simulate IPV versus time curves under standard conditions and for perturbed values of effective peritoneal surface area, peritoneal UF-coefficient, glucose mass-transfer area coefficient (MTAC or PS), dialysate volume, etc. Model parameters for these computer simulations are based on a "three-pore" model of membrane selectivity presented previously and derived from capillary physiology [12–15]. This model has proven to be a useful tool for describing transvascular and transperitoneal exchange of small and large solutes. According to the model the peritoneum behaves as a membrane having a large number of "small pores" (radius 40 to 60 Å), accounting for 90 to 95% of the total hydraulic conductance (UF-coefficient), and a very low number (1 part per 15,000 small pores) of "large pores" (radius 200 to 300 Å), accounting for approximately 5% of the peritoneal UF-coefficient [12, 13]. In addition, a third transperitoneal exchange route is predicted to exist, namely a transcellular ("ultra-small" pore) pathway, accounting for 1 to 2% of the total UF-coefficient and having an approximate pore radius of 4 to 5 Å [12, 14–16].

Methods

Theory

During a peritoneal dialysis dwell the instantaneous *net* volume flow occurring through the peritoneal membrane

$$\left(J_v \text{ or } \frac{dV}{dt} \right)$$

[1] σ is defined as the fractional "effective" osmotic pressure exerted by a solute across the membrane investigated in relation to its "ideal" osmotic pressure as established for a perfectly semipermeable membrane.

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can be described according to the following phenomenological equation [17]:

$$\frac{dV}{dt} = J_v = L_pS(\Delta P - \sigma_{prot}\Delta\pi_{prot} - \sigma_g\Delta\pi_g \sum_{i=1}^{n} \sigma_i\Delta\pi_i) - L \quad (1)$$

where L_pS has been defined above and where ΔP represents the mean hydrostatic pressure difference between the blood capillaries and the peritoneal cavity. $\Delta\pi_{prot}$ is the transperitoneal colloid osmotic pressure difference caused by the plasma proteins, and σ_{prot} and σ_g represent the average osmotic reflection coefficients for total protein and glucose across the peritoneum, respectively. $\Delta\pi_g$ is the ideal peritoneal crystalloid osmotic pressure difference exerted by glucose across a semipermeable membrane. The fourth term in the parenthesis denotes the sum of all other "effective" crystalloid osmotic gradients acting across the peritoneal membrane. Finally, L represents the lymph flow from the peritoneal cavity to the blood, whereas V stands for volume and t for time.

The crystalloid osmotic pressure differences acting across the peritoneal membrane initially after infusion of a (glucose) dialysis solution into the peritoneal cavity, $\Delta\pi_g$ and,

$$\sum_{i=1}^{n} \Delta\pi_i$$

will dissipate exponentially with time due to solute diffusion across the membrane [8–11, 18]. Hence, equation 1 contains several exponential crystalloid osmotic pressure terms, having the "lumped" rate constant "k" (min^{-1}). The other terms, (ΔP, $\sigma_{prot}\,\Delta\pi_{prot}$, and L) will, however, remain more or less constant over time during a dwell.

Assuming that equation 1 contains one "lumped" exponential term, describing the dissipation of the effective osmotic gradients acting across the peritoneum, and a number of constants, it can be integrated analytically [18] yielding:

$$V_t = V_o + a_1(1 - e^{-kt}) - a_2t \quad (2)$$

where V_t represents the drained dialysate volume, expressed as a function of time. V_o is the volume instilled at time zero, and a_1, a_2 and k are some *arbitrary* coefficients that determine the change occurring in V_t as a function of time.

Stelin and Rippe [8] showed that if glucose acts as the major crystalloid osmotic agent during CAPD, which is a reasonable assumption, then

$$a_1 \propto \frac{L_pS\ \sigma_g}{PS_g} \Delta C_{g_o}\overline{V} \quad (3)$$

where PS_g is the glucose mass transfer area coefficient (MTAC), ΔC_{g_o} is the transperitoneal glucose concentration gradient existing at time zero and $\overline{V}$ represents the mean i.p. volume during the dwell. The coefficient a_1 represents the maximal fluid volume that can be transported into the peritoneal cavity by glucose-induced osmosis during a dwell, when both lymphatic and capillary fluid absorption to the blood are set to zero. Thus a_1 describes the "height" of the V_t (or IPV) versus time curve. Furthermore, "k" approximately equals $PS_g/\overline{V}$. It was also shown previously [8] that the time at which the V_t curve peaks (t_{peak}) is inversely proportional to "k", or in terms of PS and $\overline{V}$:

$$t_{peak} \propto \frac{\overline{V}}{PS_g} \quad (4)$$

Note also that the absorption of fluid from the peritoneal cavity to the blood (a_2) is dependent on the sum of the peritoneal lymph flow (L) and the capillary fluid absorption due to L_pS and the capillary "Starling forces", that is, the "effective" transperitoneal colloid osmotic pressure difference and the transperitoneal hydrostatic pressure difference [8, 12, 19, 20]:

$$a_2 = L_pS\ (\sigma_{prot}\Delta\pi_{prot} - \Delta P) + L \quad (5)$$

Table 1. Parameters used for computer simulations of V(t) versus time curves according to a three-pore model of membrane selectivity

Small pore radius (r_s)	47 Å
Large pore radius (r_L)	250 Å
Fractional small pore UF-coeff (α_s)	0.935
Fractional transcellular UF-coeff (α_c)	0.015
Fractional large pore UF-coeff (α_L)	0.050
Fractional large pore surface area	0.002
Mol radius of sodium (and chloride)	2.3 Å
Mol radius of urea	2.6 Å
Mol radius of glucose	3.7 Å
Mol radius of albumin ("total protein")	35.5 Å
UF-coefficient (L_pS)	0.082 ml/min/mm Hg
Osmotic conductance to glucose ($L_pS\ \sigma_g$)	3.5 µl/min/mm Hg
Unrestricted pore area over unit diffusion distance ($A_o/\Delta x$)	27,000 cm
PS (MTAC) for glucose	15.5 ml/min
Peritoneal lymph flow (L)	0.3 ml/min
Transperitoneal hydrostatic pressure gradient (ΔP)	9 mm Hg
Transperitoneal oncotic pressure gradient ($\Delta\pi_{prot}$)	22 mm Hg
Dialysis fluid volume instilled	2,050 ml
Peritoneal residual volume	300 ml
Serum urea conc	20 mmol/liter
Serum sodium (and corresponding anion) conc	140 mmol/liter
Dialysis fluid sodium conc	132 mmol/liter
Serum glucose conc	6.5 mmol/liter

Reflection coefficients for all solutes in the transcellular pathway were set to 1. A majority of simulations were performed for 3.86% glucose in the dialysis fluid infused.

Computation techniques

In this paper we have tested the validity of equations 2 to 5 by *numerically* integrating equation 1 using a personal computer (Casio FX-860 P). A step-wise iterative procedure was employed for the integration, using the parameters listed in Table 1. Parameter values including those for $\Delta\pi_{prot}$, ΔP, L and L_pS were taken from our previous studies [8, 12]. Crystalloid osmotic gradients for glucose, urea, sodium and "sodium anions" (lactate, chloride) were taken into account, but those for potassium, magnesium, phosphate, etc., were neglected.

The iterative procedure followed included: 1) computation of the i.p. concentrations of glucose, urea and sodium (+chloride) at the start of a short time interval (Δt) of iteration (1 min); 2) assessment of the transperitoneal volume flow (J_v) during that period; 3) computation of the increment in peritoneal volume (ΔV) during Δt; 4) calculation of the new IPV [$V(t + \Delta t)$]; and 5) starting a new iteration. Each iteration step can be described by:

$$V(t + \Delta t) = V(t) + L_pS\ \Delta t[\Delta P(V) - \sigma_{prot}\Delta\pi_{prot} - \sigma_g\Delta\pi_g(t) - \sigma_u\Delta\pi_u(t) - \sigma_{Na}\Delta\pi_{Na}(t) - \sigma_{an}\Delta\pi_{an}(t)] - L\ \Delta t \quad (6)$$

where u, Na and an stand for urea, sodium and its anions (chloride and lactate), respectively. With negligible error, the sum of the last two crystalloid osmotic transients within parenthesis can be numerically treated as twice the sodium osmotic transient. This approach was taken in this study. The crystalloid osmotic gradients included in equation 6, that is, $\Delta\pi_g$, $\Delta\pi_u$, $\Delta\pi_{Na}$ and $\Delta\pi_{an}$, all change with time during the course of the dialysis (see eq. 9) as indicated in the equation. The change in ΔP (in mm Hg) with intraperitoneal volume (V) in this study [denoted $\Delta P(V)$] was simulated according to the relationship between intraperitoneal pressure and dialysate volume obtained by Twardowski et al for the sitting position [21]:

$$\Delta P(V) = \Delta P(V_o) - \frac{V_t - V_o}{490} \quad (7)$$

where $\Delta P(V_o)$ was set to 9 mm Hg and V_o to 2,050 ml. Furthermore, according to van't Hoff's law the ideal crystalloid osmotic gradients acting across the peritoneal membrane are related to the transperitoneal concentration gradients by:

$$\Delta\pi = RT[C_P - C_D(t)] \quad (8)$$

where RT is the product of the gas constant and the temperature in degrees Kelvin (19.3 mm Hg/mmol/liter) and where C_P is the plasma solute concentration and C_D the concentration of solute in the dialysate as a function of time.

Initial (t = 0) i.p. solute concentration [$C_D(0)$] was calculated from the solute concentration in the dialysis fluid prior to instillation (C_{DS}), the plasma solute concentration (C_P) and also from the residual i.p. volume (V_R) and the dialysis fluid volume (V_o):

$$\frac{V_o \cdot C_{DS} + V_R \cdot C_P}{V_o + V_R} = C_D(0) \quad (9)$$

The alterations in C_D with time [$C_D(t)$] was obtained from simple mass balance considerations. During a short time interval (Δt) the change in C_D for either glucose, urea or sodium chloride [from $C_D(t)$ to $C_D(t+\Delta t)$] is obtained from:

$$V(t + \Delta t) \cdot C_D(t + \Delta t) = C_D(t) \cdot V(t) + Cl(C_P - C_D(t))\Delta t \quad (10)$$

where V(t) here includes the residual volume (V_R) and where Cl is the "unidirectional" peritoneal clearance of solute (12) as defined by:

$$Cl = \frac{J_{V_s}(1 - \sigma_s)}{1 - e^{-Pe}} \quad (11)$$

In this non-linear [22] flux equation, as modified to describe unidirectional transport, Pe is a modified Peclet number, that is, $Pe = J_{V_s}(1 - \sigma_s)/PS$ and σ_s is the osmotic small pore reflection coefficient of the solute (eq. 13). During control, small solute PS values, with the exception of PS for glucose, were calculated for an "unrestricted" pore area over unit diffusion distance ($A_o/\Delta x$) of 27,000 cm consistent with current results from peritoneal equilibration tests (PET) [1, 23]. PS for glucose had to be increased from 10.2 ml/min (as predicted for $A_o/\Delta x$ = 27,000) to 15.5 ml/min to make experimental data fit the model. J_{V_s} is the transperitoneal volume flow occurring through small pores [12] as obtained by:

$$J_{V_s} = \alpha_s L_p S[\Delta P(V) - \sigma_{prot,s}\Delta\pi_{prot} - \sigma_{g,s}\Delta\pi_g(t) - \sigma_{u,s}\Delta\pi_u(t) - 2 \cdot \sigma_{Na,S}\Delta\pi_s(t)] \quad (12)$$

where s stands for small pores, and where α_s is the fraction of total hydraulic conductance accounted for by small pores. In a similar way, the large pore and the transcellular volume flows, J_{V_L} and J_{V_c}, can be obtained [12] by inserting the appropriate values of α (*fractional* hydraulic conductance) and σ for every solute and pore size (compare with Table 1).

Osmotic reflection coefficients were calculated from the expression [24]:

$$\sigma = 16/3\gamma^2 - 20/3\gamma^3 + 7/3\gamma^4 \quad (13)$$

where γ is solute radius over pore radius for either small or large pores. σ for the transcellular (ultra-small pore) pathway was set to unity for all solutes considered. For the three-pore model employed here the average reflection coefficients for the entire heteroporous membrane (in eq. 1) due to small pore (s), large pore (L) and transcellular (c) partial σ's, respectively, are weighted by the respective fractional hydraulic conductances accounted for by either pore system, that is, by α_s, α_L and α_c. Thus (since σ_c = 1):

$$\sigma = \alpha_c + \alpha_s\sigma_s + \alpha_L\sigma_L \quad (14)$$

This treatment of transperitoneal fluid transport using lumped reflection coefficients is equivalent to using equation 1 (omitting L) separately for either of the peritoneal fluid conductive pathways (compare with eq. 12) and then summing up the *partial* volume flows (J_{V_s}, J_{V_L}, J_{V_c}) and the lymph flow (L) to obtain the net fluid flow (J_V) across the peritoneal membrane.

The dialysate osmolality was calculated as the sum of the computed i.p. glucose, urea and twice the sodium concentrations in the dialysate. It was then assumed that sodium chloride and sodium lactate are fully dissociated compounds, which is not quite correct. On the other hand, we did not take into account the presence of i.p. calcium, magnesium, etc., so the total dialysate osmolality will hardly be overestimated.

Results

Control conditions

Effects of variations of the glucose concentration in the dialysis solution. Figure 1 shows computer simulated drained volume versus time [V(t)] curves obtained by varying the glucose concentration in the dialysis solution and using the parameters listed in Table 1. Setting PS for glucose at 15.5

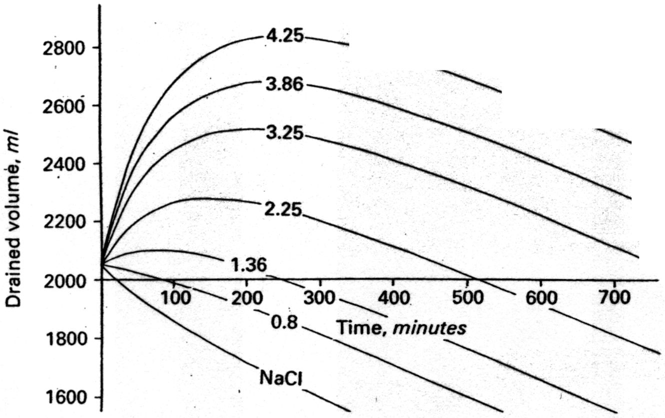

Fig. 1. *Computer simulated drained volume versus time [V(t)] curves for varying glucose concentrations in the dialysate.* Parameters used for the simulations are listed in Tables 1 and 2. Glucose concentrations in the dialysis solution infused are varied from zero (NaCl curve) to 4.25%.

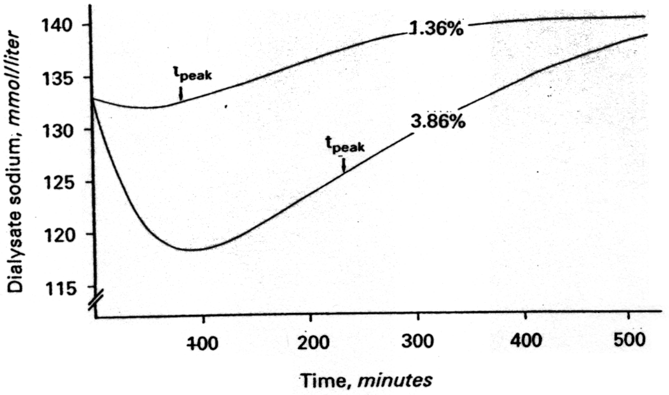

Fig. 2. *Computer simulated sodium concentration in the dialysate as a function of dwell time for 1.36 per cent (upper curve) and 3.86% (lower curve) glucose dialysis solutions during control conditions.* Initial dialysate sodium concentration (after mixing of the dialysis fluid with the residual volume) is 133 mmol/liter and that in plasma is 140 mmol/liter (Table 1). Peak times (t_{peak}) of the corresponding V(t) curves (Fig. 1) are also indicated in the figure.

ml/min makes the curves fit nearly exactly to our previously published experimental drained volume versus time relationships for 3.86 and 1.36% glucose in the dialysis solution [8]. The value of glucose PS of 15.5 ml/min was employed for control conditions throughout this study. This rather "high" PS_g as selected to fit the model to our previous data is discussed below.

In the figure, the glucose concentration in the dialysis solution (prior to instillation) is altered from zero (NaCl curve) to 4.5%. The V(t) curves largely follow the predictions of equation 3. Thus it is mainly the "height" of the curves (a_1) that increases with increasing glucose concentration and ΔC_{g_0}. To a lesser extent, however, the time at which the V(t) curves peak (t_{peak}) also increases with increasing dialysate glucose concentration.

Dialysate sodium, glucose and total osmolality versus time during cycles with either 1.36 or 3.86% glucose in the dialysis fluid. Due to the heteroporous nature of the peritoneal membrane such as predicted by the present three-pore model, a considerable fraction (40 to 50%) of the transperitoneal osmotic fluid flow induced by a large glucose osmotic gradient will occur through the "ultra-small pore" (transcellular) peritoneal pathway. Thus, even though the peritoneal membrane is highly permeable to small solutes, there will be a sieving of small solutes (mainly sodium chloride) across the peritoneum during the first few hours of the dwell. This is illustrated in Figure 2. This figure depicts the computer simulated sodium concentration in the dialysate as a function of time for 1.36 or 3.86% glucose in the dialysis fluid. Plasma sodium concentration is set at 140 mmol/liter.

Note that the sodium concentration in the dialysate reaches a minimum (of 118.5 mmol/liter) at 90 minutes for the 3.86% (glucose) dialysis fluid and of 132 mmol/liter at approximately 50 minutes for the 1.36% solution, respectively. Furthermore, for the 3.86% solution the dialysate sodium concentration lies below that in plasma during more than nine hours of the dwell! This general pattern is very close to that recently reported by Heimbürger et al [7] during 3.86% Dianeal® dwells in CAPD patients. The "normal" patients in that study reached a minimum dialysate sodium concentration after 90 min of the dwell of approximately 120.5 ± 3.5 (±SD) mmol/liter.

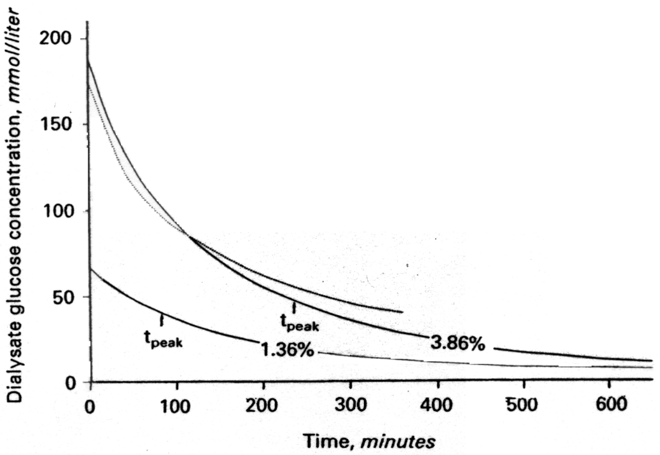

Fig. 3. *Simulated dialysate glucose concentrations versus dwell time during 3.86% and 1.36% (glucose) dwells under control conditions.* The 1.36% curve is identical to that recently published for the "distributed transport model" by Seames et al [26]. The 3.86% curve deviates from that measured in CAPD patients having "normal" UF-characteristics by Heimbürger et al [7] (dotted line). Peak times of the corresponding V(t) curves (t_{peak}) are indicated in the figure.

The computer simulated reductions in dialysate glucose concentration versus time for 1.36% and 3.86% glucose dialysis fluid dwells, respectively, are shown in Figure 3. For the 3.86% solution measured values for normal CAPD patients from the study of Heimbürger et al [7] are indicated by a dotted line. The simulated curve for the 1.36% solution is (nearly) identical to that calculated using a "distributed model" [25] of fluid and mass transfer, such as that recently published by Seames, Moncrief and Popovich [26]. From the mentioned study and the present one it seems evident that both the present (parallel pathway) model and distributed models *underestimate* the i.p. glucose concentration after approximately 120 minutes of the

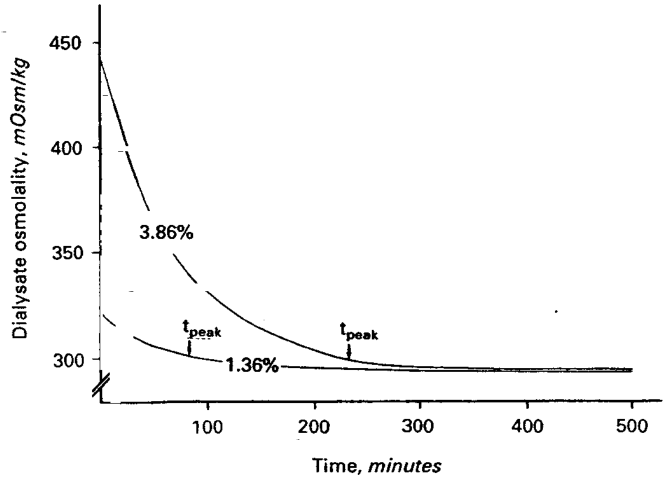

Fig. 4. *Simulated dialysate osmolality over dwell time during control conditions for 3.86% (upper curve) and 1.36% (lower curve) glucose dialysis solutions, respectively.* Curve peak times (t_{peak}) are indicated in the figure.

dwell. Note also that the t_{peak} occurs long before the i.p. glucose concentration reaches plasma values.

As presented in Figures 2 and 3, the i.p. glucose and sodium chloride concentrations both fall during the first 60 to 90 minutes of the dwell. Later during the cycle, the concentration of sodium and its anions (chloride and lactate) will increase while there is a continuing fall in i.p. glucose concentration. Hence, the initial rapid fall in dialysate osmolality, partly occurring due to dilution, partly due to glucose diffusion, slows down considerably after 50 to 90 minutes. This is illustrated in Figure 4, showing the simulated dialysate osmolality versus time for 1.36% and 3.86% (glucose) dialysates. The general pattern shown here agrees well with that measured in normal CAPD patients [7, 11].

Effects on i.p. volume versus time [V(t)] curves of variations of peritoneal surface area (S)

The effective peritoneal exchange surface area may increase in CAPD patients due to, for example, capillary "recruitment," implying that the number of effectively perfused capillaries is increased. This is usually seen in inflammation (compare with peritonitis). Decreases in S may occur due to, for instance, formations of peritoneal adhesions.

Figure 5 demonstrates the effect of altering the peritoneal surface area on V(t) curves simulated for 3.86% glucose in the dialysis fluid, from control, as denoted in the curve by "1.0," up to 10 times control and down to 0.1 times control. Note, that despite large variations in S, the height of the curves (a_1), as predicted from equation 3, is relatively well maintained. This is probably because S is part of both the numerator and denominator of the expression to the right in equation 3. However, since the t_{peak} is inversely related to PS_g (equation 4), it will decrease with increasing peritoneal surface area. Thus the theoretical predictions made from equation 3 and 4 are in good agreement with the results of the computer assisted numerical integration of equation 1 when S is varied within a wide range.

Effects of variations in peritoneal UF-coefficient (L_pS)

According to equation 4, changes in L_pS will not significantly affect the t_{peak}. However, according to equation 3 the height of the V(t) curves should be highly dependent on L_pS. This is illustrated in Figure 6, showing the computer simulated results of varying L_pS on V(t) curves for 3.86% glucose in the dialysis fluid. L_pS is varied from 0.082 ml/min/mm Hg (control or "1.0") in the range of 0.1 to 1.7 times control. Note how small variations in L_pS markedly affect the height of the curves. Increases in L_pS implies increases both in the initial UF-rate and in the peritoneal-to-blood absorption rate (a_2) ensuing upon the curve peak (compare with eq. 5).

Effects of variations in PS ("MTAC") for glucose PS_g

Increasing PS for glucose, while keeping L_pS at 0.082 ml/min/mm Hg, will, according to equations 3 and 4, reduce both the t_{peak} and the curve height (a_1). This is illustrated in Figure 7 showing the computer simulated results for 3.86% glucose when PS for glucose is perturbed from control (15.5 ml/min denoted "1.0") to range from 0.5 to 3 times control. Note that an increased PS_g will markedly reduce the volume ultrafiltered during a 240 to 300 minutes (4 hr to 5 hr) dwell. The pattern of V(t) alterations seen when PS_g is increased relative to L_pS apparently mimics that shown by a certain number of patients who have been on CAPD for several years (3 to 7). Thus, quite few patients will present a reduced UF-capacity on long-term CAPD treatment.

Effects of variations in dialysis fluid volume (V_o) and in peritoneal residual volume (V_R)

The computer simulated results of varying the fluid volume instilled for 3.86% glucose in the dialysis fluid when peritoneal residual volume is set to 300 ml, are shown in Figure 8. Again there is good agreement between simulations and theoretical predictions according to equations 3 and 4. Thus, an increased $\overline{V}$ will increase both a_1 and t_{peak}. Control curve is obtained for an instilled volume of 2,050 ml (2.05 liter), and curves simulated for infused volumes ranging from 1,050 ml (1.05 liter) up to 3,050 ml (3.05 liter) are shown for comparison.

Altering the residual volume will affect the transperitoneal glucose concentration at time zero (ΔC_{g_0}) as well as the total intraperitoneal volume. Thus, changing the residual volume would, according to equations 3 and 4, affect both the height of the curves and the t_{peak}. This is shown in Figure 9, where the i.p. residual volume is varied from 0 to 1,500 ml for an instilled volume is 2,050 ml and a glucose concentration in the dialysis fluid of 3.86%.

Effects of variations of peritoneal lymph flow (L)

An increased lymph flow partly offsets the dialysate's potential of removing body fluid by ultrafiltration (osmosis) during PD. In Figure 10 the computer simulated results of increasing L from 0 ml/min via "control", that is, 0.3 ml/min [8, 19, 27], to 2 ml/min [28, 29] during a 3.86% Dianeal® dwell is depicted. With this increase in L the total rate of fluid absorption from the peritoneal cavity to the blood increases from 0.90 to 2.9 ml/min, making the curve tails become steeper with increasing lymph flows. This pattern of V(t) alterations towards a reduced capacity of UF is different from that seen when PS for glucose alone

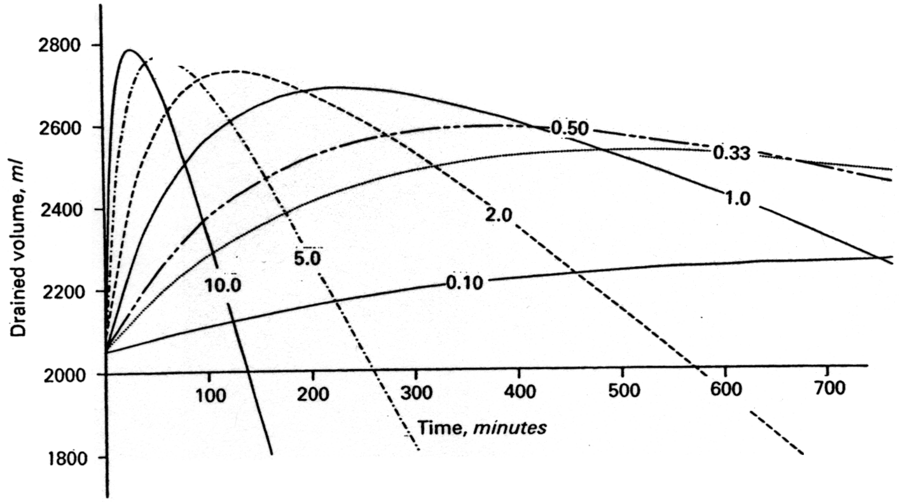

Fig. 5. *Simulated V(t) curves as a function of surface area (S) (eq. 3).* Curves are simulated for 3.86% glucose in the dialysate. Control curve is denoted "1.0". Surface area is varied from 0.1 times control (denoted "0.10") to 10 times control (denoted "10.0").

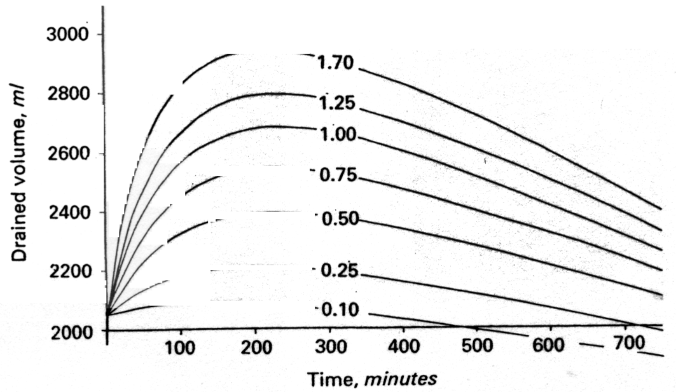

Fig. 6. *Effect of varying L_pS from 0.1 times control (denoted 0.10) to 1.7 times control (denoted 1.70) on simulated V(t) versus time curves for 3.86% glucose in the dialysate infused.*

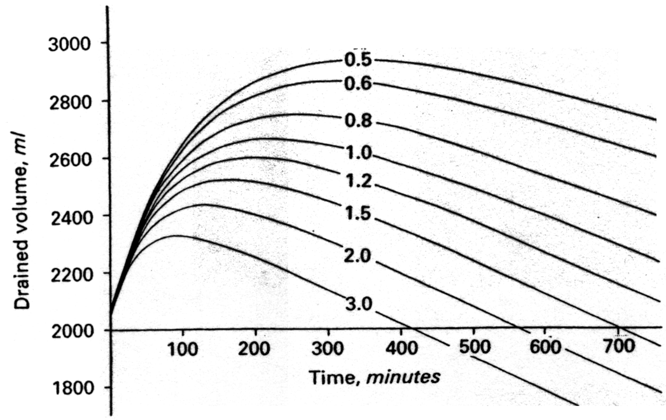

Fig. 7. *Effects of varying PS for glucose (PS_g) from 0.5 times control to 3 times control.* Control curve (denoted 1.0) is generated for 3.86% glucose in the dialysate.

is increased. However, as shown previously [8], when the total peritoneal to blood absorption rate remains unaltered at control (≈1.2 ml/min), then only a limited range of L values is theoretically possible (0.3 to 0.7 ml/min) under the provision that the peritoneal membrane "sieving coefficients" for small solutes are ≥ 0.3 [8].

Theoretical result of varying the small pore radius (r_s)

Inflammatory increases in microvascular permeability are usually the result of the formation of interendothelial gaps (large pores), preferentially in venular endothelium, caused by inflammatory mediators, such as histamine-type mediators and/or cytokines [30, 31]. It can be shown that large pore formation would not markedly affect the IPV versus time curves. Furthermore, the small pore system is usually not significantly affected by inflammation [30, 32]. Still it would be of theoretical interest to study how variations in r_s would affect the V(t) curves.

In Figure 11 the small pore radius is increased from 36 Å, via 47 Å (control curve) to 80 Å, keeping the total pore area over unit diffusion distance ($A_o/\Delta x$) constant at 27,000 cm. Again the simulations are made for 3.86% glucose in the dialysate. Note that the t_{peak} will be reduced when r_s is increased, whereas there is a tendency that the height of the curves (a_1) increase. This follows from equations 3 and 4. Increasing r_s will increase L_pS more than PS_g, since L_pS is related to the fourth power of r_s according to Poiseuille's law, while PS_g is related to r_s (via S) by its second power. Furthermore, σ_g is related to r_s by equation 12. Thus, when r_s is increased, the numerator of the expression to the right in equation 3 will in most instances increase more than the denominator, provided that the fall in σ_g is small, and hence, a_1 is increased. Furthermore, when r_s increases, then PS will increase, and hence, the t_{peak} is reduced.

Effects of simultaneously increasing peritoneal surface area (S), the number of large pores (n_L) and the peritoneal lymph flow (L)

During peritonitis the V(t) curves usually peak early (the t_{peak} is reduced). The height of the V(t) curves may decrease, increase or remain unchanged [4, 33, 34]. These changes may be simulated by simply increasing the number of effectively perfused capillaries, implying increases in the peritoneal surface

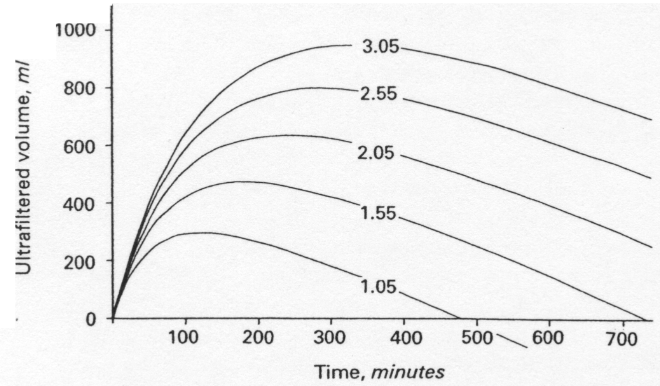

Fig. 8. *Simulated ultrafiltered volume versus dwell time as a function of instilled dialysate volume, as varied from 1,050 ml to 3,050 ml.* Control curve is generated for an instilled volume of 2,050 ml and a dialysate glucose concentration of 3.86%. Residual volume is 300 ml.

area (S). The effect of increasing S alone has been demonstrated in Figure 5. In peritonitis vascular permeability is also increased and, as mentioned above, this is usually due to an increase in large pore number, which will greatly enhance the leakage of proteins from the blood to the peritoneal cavity [30–33]. Furthermore, lymph flow (L) is expected to increase.

In Figure 12 simulations of V(t) curves are made for both 1.36% and 3.86% glucose in the dialysate. S is here increased by 70%. The ratio of large pore to small pore number is increased one order of magnitude (from 1/14,970 to 1/1,497). L is either unchanged at 0.3 ml/min (hatched line) or is increased to 1 ml/min (dotted line). Control curves for 1.36 and 3.86% glucose are represented by solid lines. As a result of these perturbations (regardless of the assumptions for L), L_pS was found to increase from 0.082 to 0.201 ml/min/mm Hg and α_L increased from 0.05 to 0.35. Furthermore, α_s dropped from 0.935 to 0.64 and α_c decreased from 0.015 to 0.010. According to equation 14, σ for glucose (σ_g) decreased from 0.043 to 0.030 and σ for Na dropped from 0.026 to 0.018. Simultaneously, σ for albumin fell from 0.90 to 0.64. Somewhat surprisingly, the shape of the IPV versus time curves was only little affected by the increase in large pore number.

Increasing the surface area (S) further than in this example will make the V(t) curves peak even earlier, and the steepness of the curve tails will increase further. If PS for glucose increases out of proportion to L_pS, then the curve height (a_1) will tend to decrease. The specific example of changes in peritoneal exchange parameters compatible with peritonitis depicted here is, of course, just one of many possibilities. Increases in S, conceivably through recruitment of capillaries, seem, however, to play a key role in peritonitis, leading to a "leftward" displacement of the V(t) curves and an increased rate of fluid absorption (a_2) from peritoneum to blood.

Discussion

The present computer simulations of the variations in drained peritoneal dialysate volume as a function of time, V(t), during a single PD cycle are based on a three-pore model of peritoneal permselectivity. This model is founded on current concepts valid for transmicrovascular transport. The main elements of this heteroporous model are: the small pore (paracellular pathway) radius (r_s), the peritoneal UF-coefficient (L_pS), the fractional UF-coefficient accounted for by small pores (α_s) and by a transcellular fluid conductive pathway (α_c), respectively, and the glucose permeability-surface area product (PS_g or $MTAC_g$). To be able to model the absorption of fluid from the peritoneal cavity to the blood occurring after three to six hours, assumptions had also to be made concerning the peritoneal lymph flow (L) and the capillary "Starling forces" (ΔP and $\sigma_{prot}\, \Delta\pi_{prot}$). The major non-membrane parameters determining transperitoneal fluid exchange are: the volume and glucose concentration of the dialysate instilled (mass of glucose administered) and the residual intraperitoneal volume. Changes in large pore number of radius, at least within the range expected during inflammation, were not, however, found to markedly affect the peritoneal fluid balance. Neither did fluctuations of plasma solute concentrations (urea, glucose or sodium) within ±5 mmoles/liter have any major influence on transperitoneal fluid exchange.

The computer assisted numerical integration of the functions describing the instantaneous transperitoneal volume flow

$$\left(\frac{dV}{dt} \text{ or } J_V\right),$$

generated V(t) curves which were in good agreement with predictions based on (approximate) analytical integrations of

$$\left(\frac{dV}{dt}\right)$$

[8]. Thus, the height of the V(t) curves, a_1, proved to be dependent on the ratio of L_pS to PS_g as well as on the glucose concentration and of the volume of the infused dialysis solution. Hence, the height of the curves is largely independent of peritoneal surface area. Furthermore, the peak time of the V(t) curves, was found to be inversely proportional to the PS_g but directly proportional to intraperitoneal fluid volume. These predictions follow directly from equations 3 and 4.

There are several interesting implications of equations 3 and 4. For example, in children, the V(t) curves for any dialysis fluid glucose concentration would peak earlier than in adults, mainly due to the lower volume of the solution infused. Even though the PS_g would also be lower in children than in adults, the ratio

$$\frac{\overline{V}}{PS_g}\left[\frac{\text{volume}}{\text{area}} = \frac{(\text{length scale})^3}{(\text{length scale})^2}\right]$$

would actually be lower too. Hence, the t_{peak} must be reduced in children (eq. 4), as is also generally observed clinically [35]. An increased L may, however, also contribute to the reduced t_{peak} seen in children [35].

During peritonitis IPV versus time curves often show changes which are compatible with increases in *both* small solute PS (and PS_g) and in L_pS. Inasmuch as PS_g and L_pS are increased to the same extent, these alterations comply with an increased surface area (S), probably generated by inflammatory recruitment of microvessels (Fig. 5). During peritonitis PS may, however, in some cases increase more than L_pS, and in this case the curve height is markedly reduced (compare with Fig. 7). The increase of small solute PS (and PS_g) occurring in some patients on long-term CAPD treatment are usually also not

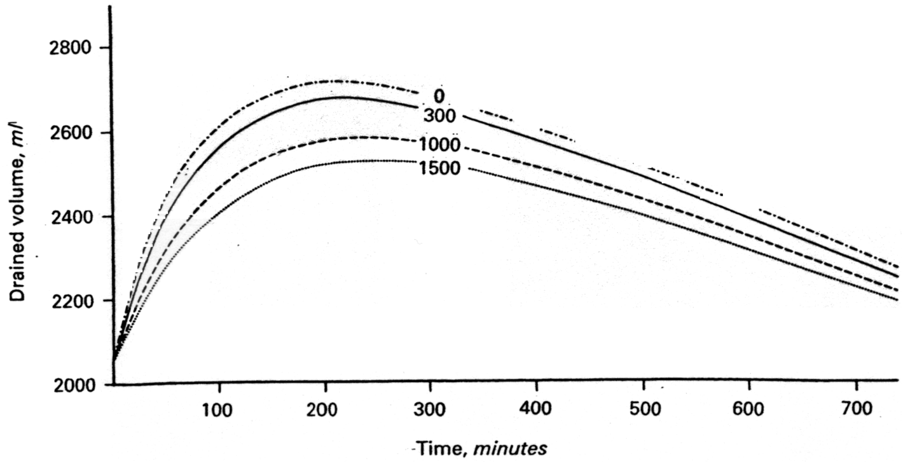

Fig. 9. *Simulated V(t) curves for variations in i.p. residual volume from 0 to 1,500 ml when 2,050 ml of 3.86% Dianeal® is instilled intraperitoneally.* Increasing the residual volume will lower the maximum curve height (a_1) and increase the t_{peak}.

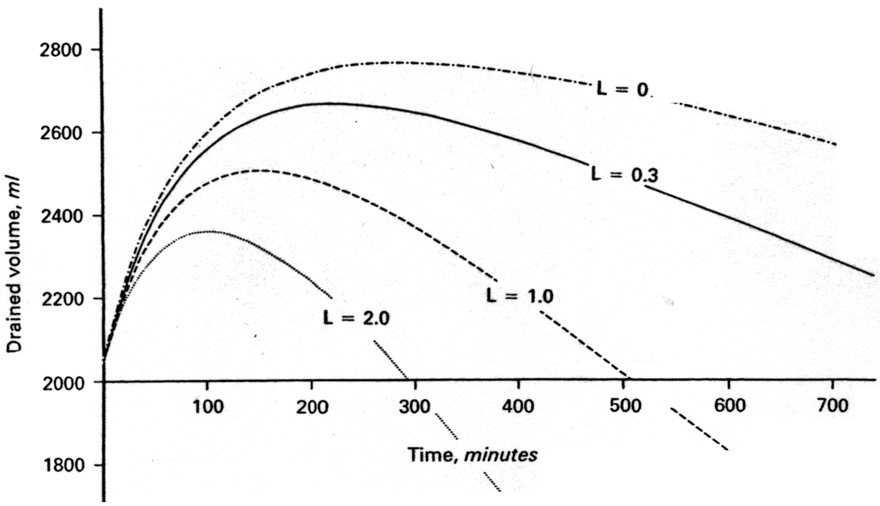

Fig. 10. *Impact of lymph flow (L) on simulated V(t) curves using 3.86% glucose in the dialysate infused.* L is varied between zero and 2.0 ml/min. "Control curve" (for L = 0.3 ml/min) is depicted by the solid line.

coupled to increases in L_pS of the same magnitude, often leading to a marked loss of UF-capacity.

The present model is a "lumped parameter" model treating the blood-peritoneal barrier as a simple membrane analogous to continuous capillary walls. This membrane is assumed to contain two major fluid conductive pathways coupled in parallel, small (paracellular) pores and ultra-small (cell membrane) pores, and a third parallel pathway, large pores, permitting macromolecules to be filtered to the interstitium. The large pore pathway is, however, of negligible importance for fluid transport driven by crystalloid osmosis. More sophisticated models also take into account transport resistances coupled in series. Thus, considering the major peritoneal barrier to be the capillary walls, they also include the interstitium and the mesothelium [25, 26]. Such "distributed model" approaches would be more accurate than the present "single membrane" model. On the other hand they are of much greater complexity [25, 26]. Thus, the present model is easily run on a simple pocket PC.

Distributed models predict the presence of solute concentration gradients in the interstitium throughout the cycle. Hence, according to such models the crystalloid osmotic gradients acting across the capillary membrane proper will be considerably lower than modelled here. Otherwise the general predictions regarding the V(t) curves from the present model and from distributed models are similar. However, both distributed models and the present simple parallel pathway model suffer from the problem that they do not accurately predict the concentration of glucose in the dialysate over time, especially after approximately two hours of the cycle (compare with Fig. 3). The rate of dissipation of the apparent "driving" osmotic gradient across the peritoneal barrier in our model and in the distributed model of Seames et al [26] is thus considerably faster than the dissipation rate of the measured i.p. glucose concentration alone. This can only be partly explained by dilution effects following the often massive *transcellular* water movement (UF) occurring during the early phase of the cycle. Such a dilution of the dialysate gradually creates a large sodium chloride (and sodium lactate/bicarbonate) osmotic gradient (Fig. 2) across the peritoneum during the first 50 to 100 minutes of the dwell time. For 3.86% glucose in the dialysis solution, the latter gradient will after 90 minutes become approximately: $2 \cdot (140 - 118.5) \cdot 19.3 \cdot 0.03$ mm Hg ≈ 25 mm Hg ($= 2\Delta C_{Na} \cdot$

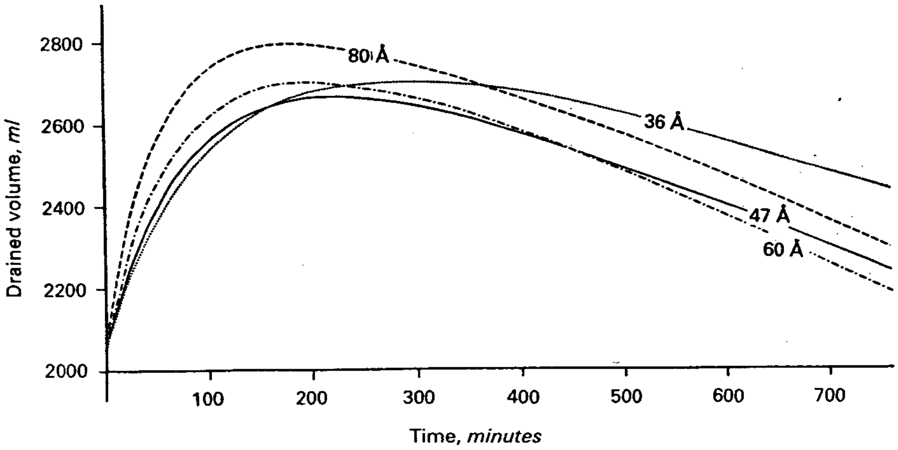

Fig. 11. *Theoretical result of varying the small pore radius (r_s) on simulated V(t) curves for 3.86% glucose in the dialysis fluid.* Control curve [r_s = 47 (Å)] is denoted by a solid line.

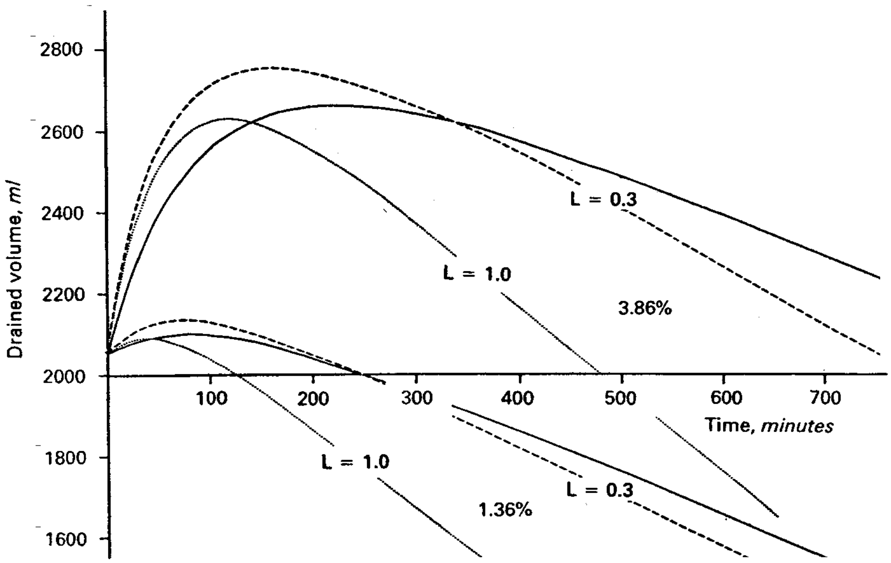

Fig. 12. *Effects of "peritonitis" on simulated V(t) curves for 3.86% glucose (upper three curves) and 1.36% glucose (lower three curves), respectively, in the dialysis fluid.* The surface area term (S) is increased by 70% and microvascular "permeability" is enhanced by increasing the relative number of large pores one order of magnitude from control. Control curves are represented by solid lines. Lymph flow is either unchanged at 0.3 ml/min (hatched lines) or increased to 1 ml/min (dotted lines).

RT · σ_{NaCl}), (compare with eq. 6 and 8) in the present simulations. This gradient initially opposes the glucose osmotic gradient, and though it cannot fully explain the rapid dissipation of the driving osmotic gradient over cycle time, it contributes to this phenomenon.

In order to fit our model to previous experimental V(t) curves during control, which reflect the mentioned rapid dissipation of the driving peritoneal osmotic gradient [8], PS for glucose in this study had to be set approximately 50% higher than predicted from our assumed value of $A_o/\Delta x$. A distributed model of peritoneal transport can account for this internal inconsistency between model parameters only if there are marked changes of the interstitial solute concentration profiles with dwell time. Interstitial gradients thus have to become progressively steeper over the course of the cycle, that is, solute transport resistances in the interstitium have to increase with cycle time. One way to conceptualize such alterations is to think of interstitial "unstirred fluid layers" that gradually build up over cycle time due to the decreasing impact over the dwell of transmembrane convection. This may at first seem speculative, but from previously published PET data [1] it seems evident that PS values for small solutes are 40 to 50% higher during the first 60 minutes of the dwell than subsequently [23]. This would support the notion that "unstirred layers" may actually contribute to peritoneal transport characteristics [2, 4] by gradually building up and enhancing the rate of dissipation of the effective crystalloid osmotic gradient over the course of the cycle. In the present model we have compensated for effects of this kind by increasing the value of PS_g above that predicted from the assumed value of $A_o/\Delta x$.

In the present simulations the peritoneum is considered to be very selective with regard to both solute transport and osmosis (UF). Hence, whereas the ratio of the *free* diffusion coefficient of glucose ($9.0 \cdot 10^{-6}$ cm²/sec) to that of albumin ($9.3 \cdot 10^{-7}$ cm²/sec) is approximately 10, the ratio of calculated "unidirectional clearances" (≈ PS values) of these solutes is over 100 (compare with Table 2) for the parameters selected and in agreement with measured clearance data [1, 5–7, 12, 18, 36]. Furthermore, σ for glucose is here 0.043 and that of albumin 0.9, although, due to the heteroporous nature of the peritoneal barrier, the glucose sieving coefficient is as low as 0.6. By contrast, Bell et al [37] found a very low degree of diffusional

Table 2. Calculated PS (MTAC) values (assessed using eq. 11 and 12 in ref. 12) and total σ's (eq. 13, 14) for some solutes as based on the parameters shown in Table 1

	PS *ml/min*	σ
Sodium chloride	18.8	0.0262
Urea	16.2	0.0293
Creatinine	13.5	0.0338
Glucose	10.2	0.0430
Albumin	0.086[a] (0.004)	0.895

$A_0/\Delta X$ is set to 27,000 cm. Note that PS_g (PS for glucose) calculated in this way is 34% lower than the value (15.5 ml/min) fitting to our previously published V(t) curves [8]. Solute radius of creatinine was set to 3.0 Å.

[a] Note that the calculated albumin "PS" here represents the "unidirectional clearance" of albumin (comprising both albumin diffusion through small pores *and* albumin convection through small and large pores) for a net transperitoneal volume flow of 1.0 ml/min (calculated according to the parameters in Table 1). For the three-pore model, a unidirectional clearance of albumin of 0.12 [12] is obtained when r_s is set at 52 Å. The pure *diffusional* albumin transport coefficient given in parenthesis is very low.

restriction in the rabbit peritoneum of the passage of different size dextrans, at variance with rabbit dextran clearance data published by others [38–40]. Yet rabbit peritoneal permselectivity with respect to osmosis (UF) was found to be unproportionally high. The sieving coefficients of dextrans across the rabbit peritoneal membrane in their study conformed to a two-pore membrane model comprising a few 300 Å "large pores", accounting for 0.3% of the total pore area, and as much as 43% of the L_pS, together with a large number of very small pores, 20 Å in radius.

We cannot find that this apparent inconsistency between osmotic and permeation barrier properties of the rabbit peritoneal membrane, exposed to extensive surgery [37], characterizes the normal *human* blood-peritoneal exchange. It may be explained by methodological differences, species differences and the use of dextrans as molecular probes for membrane selectivity in the rabbit model. Dextrans are long-chained flexible molecules that can "reptate" across pores which are smaller than the Stokes radius of the molecule itself [41].

In conclusion, the present simulations are based on a parallel pathway membrane model derived from capillary physiology, and it comprises a large number of paracellular small pores (radius $\approx$ 45 to 50 Å), accounting for 90 to 95% of the UF-coefficient, and a small number of large pores (radius $\approx$ 250 Å), accounting for $\approx$5% of L_pS, and, in addition, a "transcellular" fluid conductive pathway, accounting for 1 to 2% of L_pS. Although it is a simple "lumped parameter" model, easily handled on a pocket PC, it seems to be a useful tool for describing transperitoneal volume shifts during normal and perturbed conditions in CAPD. The presence of transcellular pores offers an explanation of the fact that small solute sieving coefficients in the peritoneal membrane during large glucose induced osmotic UF-flows are approximately 0.5 to 0.7 [42], and not near unity, as predicted by a strict two-pore model [12]. Furthermore, in the present simulations, the peritoneal lymph flow (L) was less than 0.5 ml/min, which is consistent with a description of the peritoneal fluid exchange during CAPD in line with current hydrodynamic theories [8].

Acknowledgments

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Reprint requests to Gunnar Stelin, M.D., Department of Nephrology, Sahlgranska Hospital, S-413 45 Göteborg, Sweden.

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ULTRAFILTRATION WITH AN ISOSMOTIC SOLUTION DURING LONG PERITONEAL DIALYSIS EXCHANGES

C. D. MISTRY N. P. MALLICK
R. GOKAL

Department of Renal Medicine, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL

Summary The potential of a starch-derived glucose polymer (molecular weight 16 800) as an osmotic agent for peritoneal dialysis was evaluated. A dialysate isosmotic to uraemic serum (302 [SEM 1·3] mOsm/kg) containing 5% glucose polymer (9·4 mmol/l) was compared with hypertonic (332 [1·0] mOsm/kg) 1·36% glucose (76 mmol/l) solution for ultrafiltration, solute transport, and carbohydrate absorption over 6 h and 12 h peritoneal dialysis exchanges. Glucose polymer solution produced substantially greater net ultrafiltration than glucose, while maintaining stable dialysate osmolality throughout the exchanges. At 6 h and 12 h, 14·4% and 28·1% of glucose polymer had been absorbed, compared with 61·5% and 83·0% of glucose; thus, glucose polymer provided less than 50% of the calorie load of the glucose dialysate per unit volume of ultrafiltrate. There was a 7–9-fold increase in serum maltose with glucose polymer. This high-molecular-weight glucose polymer produced sustained ultrafiltration even when dialysate osmolality remained within the physiological range, by a mechanism resembling "colloid" osmosis. It is a safe and effective osmotic agent but its long-term effects need further study.

Introduction

THE removal of excess body water (ultrafiltration) and solutes in peritoneal dialysis has always been achieved by means of dialysis solution made hypertonic to plasma by the addition of glucose as an osmotic agent. However, the rapid absorption of glucose leads to progressive dissipation of the osmotic gradient, so that effective ultrafiltration lasts for only 2–3 h.[1] This effect is of little consequence during the short dwelling time (30–60 min) of intermittent peritoneal dialysis; in continuous ambulatory peritoneal dialysis (CAPD), exchanges last for 4–8 h and reabsorption of initially ultrafiltered peritoneal fluid may occur, especially during the long overnight exchanges.[1] Furthermore, a daily absorption of 150–300 g glucose from the dialysate aggravates such long-term metabolic complications as hyperinsulinaemia, hyperlipidaemia, and obesity.[2-5] Clearly, the development of another osmotic agent capable of sustained ultrafiltration with minimum absorption is desirable.

In biological systems, where transport requirements similar to those of CAPD exist across many permeable membranes, the osmotic effectiveness of albumin (molecular weight 68 000) is well recognised. The capillary wall is freely permeable to plasma crystalloids but restricts the passage of albumin; the protein thus exerts a weak, but effective, "colloid" osmotic pressure, even though its molar concentration (0·66 mmol/l) represents a fraction of total plasma solutes (295 mmol/l). The physiological phenomenon of colloid osmosis is extremely important in maintaining sustained osmotic transport between extracellular fluid compartments of virtually identical total osmolality (isosmotic flow). The clinical application of this phenomenon to CAPD would have the major advantage of sustained ultrafiltration in the presence of an isosmotic dialysis fluid.

Although human albumin would be an ideal osmotic agent, its high manufacturing cost prohibits its widespread clinical use. Non-physiological macromolecules, such as dextran, polyanions, and gelatine cause difficulties with allergenicity, hyperviscosity, and peritoneal toxicity.[6-8] A soluble polymeric form of glucose (glucose polymer) readily isolated by fractionation of hydrolysed corn starch may be a potentially useful agent. We have investigated the ultrafiltration characteristics, solute transport, and carbohydrate absorption over single 6 h and 12 h exchanges of such a mixture of oligopolysaccharides, linked predominantly by α1–4 bonds but with some α1–6.

Patients and Methods

We studied five non-diabetic patients (four male, one female) aged 21–64 years (mean 46·0 years) whose condition had been stable on four daily CAPD exchanges for a mean period of 10·8 months (range 3–24 months) and who had had no peritonitis for at least 3 months before the study. The residual creatinine clearance was 0–2 ml/min (mean 1·3 ml/min).

A 5% solution of glucose polymer (9·4 mmol/l), containing polymer fractions of variable chain length ranging from 4 to 300 glucose units, with weight average molecular weight (Mw) 16 800 and number average molecular weight (Mn) 5000, was compared, with a commercially available 1·36% glucose solution (76 mmol/l; Travenol 'Dianeal'). The electrolyte content of the solutions was identical, except that the sodium level of glucose polymer solution was significantly greater than that of glucose solution (145 mmol/l *v* 131 mmol/l).

Each patient underwent two separate 6 h exchanges with 2 litres of dialysis fluid containing either 1·36% glucose or 5% glucose polymer. After an overnight fast of 10 h, subjects were admitted to the renal unit procedure room, dialysate was drained, and 2 litres of fresh fluid were infused by gravity over 10 min. Blood and dialysate samples were collected simultaneously before dialysis and at 0, 15, and 30 min, then at 1 h, 2 h, 3 h, 4 h, and 6 h; time zero was taken as halfway through the infusion. All subjects fasted throughout the exchange. At the end of the 6 h exchange the fluid was drained and its volume recorded. After the glucose dialysis the normal dialysis schedule restarted; after the glucose polymer exchanges dialysis was discontinued for 24 h and additional blood samples were taken at 3 h, 14 h, and 24 h. The studies were separated by 48–72 h.

Four of these patients also underwent 12 h exchanges (overnight) with identical procedures and dialysate fluids to the 6 h exchanges. In these patients blood and dialysate samples were collected only before and after the exchange.

The study was approved by the ethical committee of the Central Manchester Health Authority and written informed consent was obtained from every patient.

The serum and dialysate samples were analysed biochemically on a Vickers M3000 multichannel autoanalyser; glucose was measured by the glucose oxidase method, osmolality by freezing-point depression, and glucose polymer by gel-permeation chromatography, on 'Bio-gel P_2', with a modified Jelco 6AH automatic carbohydrate analyser and an orcinol/sulphuric acid detection system.[9]

All values are expressed as a mean (standard error of the mean). The significance of differences between the two solutions was assessed by Student's *t* test.

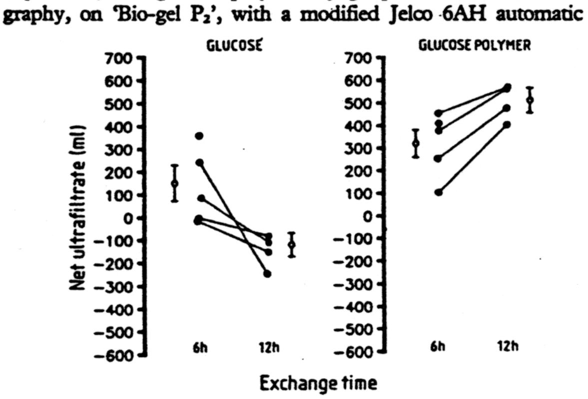

Fig 1—Net ultrafiltration at the end of 6 h and 12 h dwell for glucose (1·36%) and glucose polymer (5%) solutions.

Bars = mean ± SEM.

Results

The initial osmolality of the 1·36% glucose solution was 332 (1·0) mOsm/kg and that of 5% glucose polymer was 302 (1·3) mOsm/kg ($p < 0.001$); the glucose polymer solution did not differ significantly in osmolality from uraemic serum (300 [3·0] mOsm/kg; $p < 0.53$).

The net ultrafiltration determined by the drainage volumes at the end of the 6 h exchanges was significantly greater with 5% glucose polymer solution than with 1·36% glucose (315 [63] ml *v* 140 [70] ml; $p < 0.03$). For glucose solution increasing the exchange time to 12 h led to reabsorption of the intraperitoneal volume in all four patients, resulting in a net deficit from the infused volume (negative ultrafiltration) of 125 (43) ml; with glucose polymer solution ultrafiltration continued throughout a 12 h exchange (net ultrafiltrate 506 [48] ml; $p < 0.003$; fig 1).

The variations in total dialysate osmolality with the exchange time and the transperitoneal solute fluxes which contribute to these changes are shown in fig 2. With 1·36% glucose, the steady absorption of glucose from the peritoneal cavity exceeded the influx of solutes such as urea and

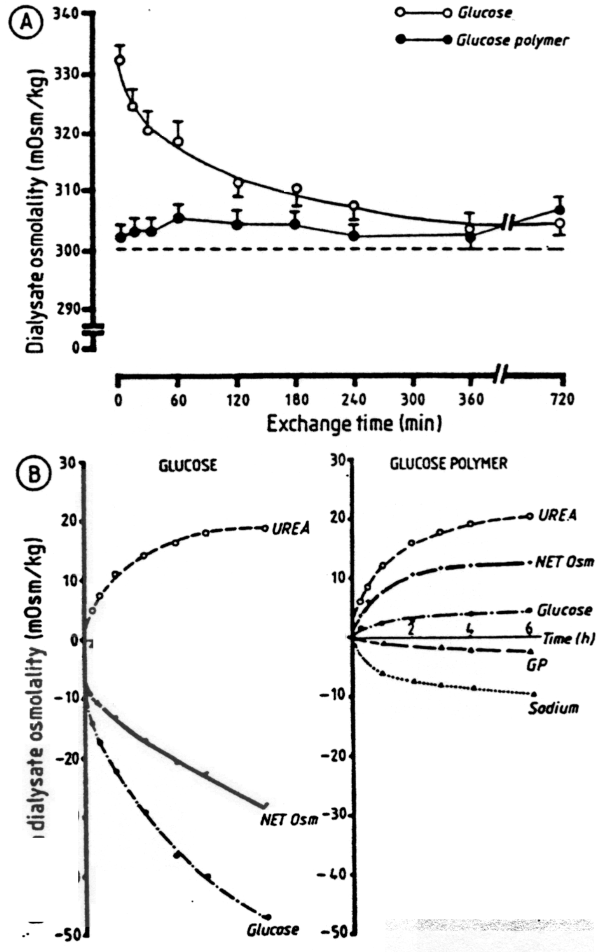

Fig 2—Relation between change in total dialysate osmolality and exchange time (A) and the principal transperitoneal solute fluxes contributing to this change (B).

GP = glucose polymer; NET Osm = net dialysate osmolality.

TABLE I—SOLUTE TRANSPORT ACROSS PERITONEUM

	Mean (SEM)					
	6 h dwell			12 h dwell		
	Glucose	Glucose polymer	p	Glucose	Glucose polymer	p
Dialysate/plasma ratio (%)						
Urea	95·0 (2·3)	98·0 (1·9)	NS	100 (8·6)	100 (1·2)	NS
Creatinine	72·8 (3·2)	80·7 (3·2)	0·03	93·0 (4·9)	97·0 (4·2)	NS
Phosphate	65·2 (3·6)	73.3 (4·8)	0·04	100 (8·3)	98·8 (4·2)	NS
Uric acid	65·1 (3·6)	75·8 (4·7)	0·04	81·0 (6·3)	97·3 (2·3)	0·03
Average peritoneal clearance (ml/min)						
Urea	6·17 (0·1)	6·69 (0·2)	0·05	3·32 (0·2)	3·58 (0·2)	
Creatinine	4·83 (0·3)	5·52 (0·4)	0·03	3·28 (0·3)	3·62 (0·1)	
Phosphate	4·25 (0·3)	5·02 (0·4)	0·04	3·17 (0·2)	3·63 (0·2)	
Uric acid	4·24 (0·3)	5·20 (0·4)	0·03	2·33 (0·2)	3·57 (0·2)	

creatinine. The net result was an exponential decline in the total dialysate osmolality. The smaller fall in osmolality associated with absorption of the polymer was more than compensated by influx of urea and other solutes and led initially to a slight rise in dialysate osmolality, which then remained stable throughout the exchange. Plasma osmolality remained unchanged during dialysis with both solutions.

Table I shows solute transport across the peritoneum, expressed as the dialysate to plasma equilibration ratio, and average peritoneal clearances. Urea diffused rapidly through the peritoneum and was fully equilibrated within 6 h with both solutions, but the larger solutes, creatinine, phosphate, and uric acid achieved greater equilibration with glucose polymer than with glucose solution; these solutes (except uric acid) were fully equilibrated within 12 h with both solutions.

The average peritoneal clearance of a solute is determined by the product of the dialysate/plasma ratio and the dialysate flow rate (drained volume per unit exchange time). The higher flow rate associated with glucose polymer solution meant that solute clearances were significantly greater than with glucose solution.

The percentage of the infused carbohydrate absorbed from the peritoneal cavity was substantially lower for glucose polymer than for glucose at 6 h (14·4% [2·6] *v* 61·5% [4·3]; $p < 0·001$) and 12 h (28·1% [3·4%] *v* 83·4% [3·4%]; $p < 0·001$), but the absolute amount absorbed, and therefore the potential calorie load per exchange, was similar at 6 h and significantly greater for glucose polymer at 12 h (table II). After correction for the differences in net ultrafiltration between the two solutions, the calorie load per ml ultrafiltrate for glucose polymer was less than half that for glucose.

TABLE II—TOTAL CARBOHYDRATE (CHO) ABSORPTION FROM PERITONEAL CAVITY AND POTENTIAL CALORIE LOAD

	6 h dwell			12 h dwell		
—	Glucose	Glucose polymer	p	Glucose	Glucose polymer	p
% of infused CHO absorbed	61·5 (4·3)	14·4 (2·6)	<0·001	83·0 (3·4)	28·1 (3·4)	<0·001
Amount (g) CHO absorbed	18·0 (1·9)	17·7 (3·2)	NS	24·9 (1·4)	37·0 (4·4)	<0·013
Total calorie load	72·6 (8·5)	71·0 (13·0)	NS	99·5 (4·9)	148·0 (15·7)	<0·013
Net ultrafiltrate (ml)	+140 (70)	+315 (63)	<0·03	−125 (43·3)	+506 (48·0)	<0·003
Calories/ml ultrafiltrate	0·52 (0·1)	0·23 (0·1)	<0·05	−0·80* (0·3)	0·29 (0·1)	<0·02

* = calorie load/ml ultrafiltrate reabsorbed.

The systemically absorbed glucose polymers are hydrolysed predominantly by the circulating amylase to the disaccharide maltose. There was a gradual rise in the level of maltose from 0·09 (0·03) mmol/l before dialysis to 0·59 (0·06) mmol/l and 0·79 (0·1) mmol/l at the end of 6 h and 12 h dialysis, respectively. These levels remained virtually unchanged when the dialysis was discontinued for 24 h. During dialysis, the glucose polymer solution, which was initially free of maltose, showed a gradual rise in maltose content to 0·34 mmol/l and 0·74 mmol/l at the end of 6 h and 12 h. These levels represent a peritoneal clearance for maltose of 3·5 ml/min. There were no appreciable changes in blood glucose or insulin levels with either solution.

One patient experienced a single episode of abdominal pain lasting 20 min during the infusion of 5% glucose polymer solution. No other adverse effects were observed.

Discussion

We have shown that a 5% glucose polymer solution, isosmotic to uraemic serum, produced sustained ultrafiltration across the peritoneal cavity for up to 12 h. The phenomenon of osmotic flow between solutions of identical total osmolality appears to be at variance with the generally recognised concept of osmotic flow along the osmolality gradient, but the importance of the effects of membrane permeability characteristics on the direction and size of osmotic forces is not well appreciated in clinical practice. The flow through an "ideal" semipermeable membrane (permeable only to water) is primarily determined by the total number of solute particles (ie, total osmolality) irrespective of their size and shape. However, the flow through a solute-permeable membrane (which is what most biological membranes are) is a function only of relatively non-permeating solutes[10,11] and therefore not necessarily related to the total osmolality of the solution, especially when the freely permeating solutes constitute a major fraction. Furthermore, the ability of solutes to permeate such a membrane is determined by molecular size and shape, as well as the solutes' deformability and ionic charges.[12] To characterise this relation between solutes and membrane, Starverman introduced a useful concept of reflection coefficient (σ) whose value ranges from zero for solutes as able to permeate as water to one for a solute that is completely non-permeating.[10,11] By incorporation of this coefficient into the basic Van't Hoff equation, the flow through any membrane, semipermeable or solute-permeable, can be expressed as

$$\text{Flow} = Lp.A[P - \Sigma^{n}_{j=1} (\sigma.C)]$$

where A = membrane area; Lp = proportionality coefficient; P = hydrostatic pressure; $\Sigma^{n}_{j=1}$ = the sum of the products of the reflection coefficients of the solutes (1 to n) and their differences in molar concentration across the membrane. The direction of osmotic forces through a membrane is, therefore, determined by the size of the sum of the products of the reflection coefficients and molar concentrations of solutes on either side of the membrane. It follows that osmotic water transport between solutions of identical osmolality may well proceed through a solute-permeable membrane if an appropriate choice is made of solutes with different reflection coefficients: this process would not occur through an ideal semipermeable membrane, where all solutes have a reflection coefficient of one.[10,11] This is the physiological basis of "colloid" osmotic flow similar to that induced by albumin across the capillary wall (fig 3).

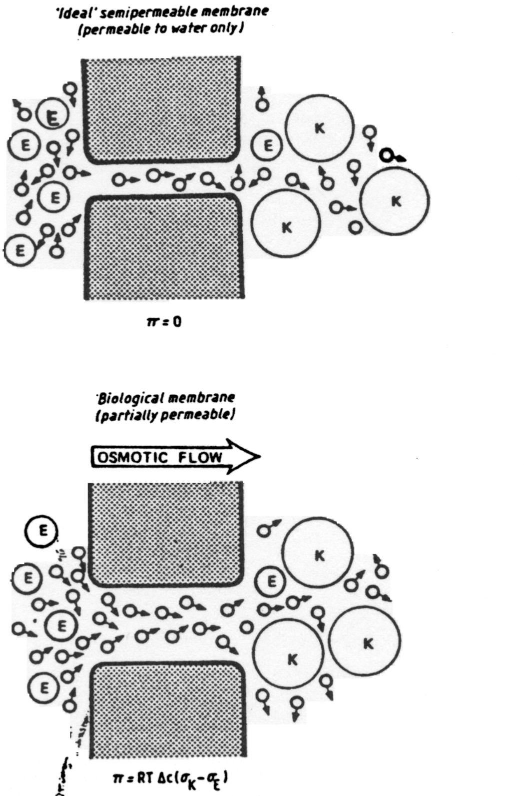

Fig 3—Diagramatic representation of osmotic flow across ideal semipermeable and partially permeable membranes separating isosmotic solutions.

E and K used to depict molecular size of solutes. σ = reflection coefficient.

The isosmotic flow in our study confirms the permeable nature of the peritoneum membrane and suggests that at this low concentration glucose polymer (9·4 mmol/l) must have a high reflection coefficient to induce such a flow. Since this process occurs with molecules less than a third the size of albumin, the effective pore size of the peritoneum must be substantially smaller than that of the capillary wall. The high reflection coefficient of glucose polymer would also account for the substantially lower percentage loss from the peritoneal cavity than with glucose. However, similar peritoneal losses have been reported for molecules larger than glucose polymer. Up to 17% of radioiodinated serum albumin (molecular weight 68 000) was lost from the human peritoneal cavity over 7 h,[13] and losses of up to 14% over 4 h have been reported[14] for molecules as large as blue dextran (molecular weight 2×10^6) from the peritoneal cavity of rabbits. These results imply that a slow but constant absorption occurs from the peritoneal cavity even when the molecular size of solute exceeds the effective size of the pores in the peritoneal membrane. This hypothesis accords with evidence for peritoneal lymphatic transport of macromolecules[15] and may have a direct bearing on the choice of an optimum size osmotic agent; increasing the molecular size beyond a certain optimum would not reduce appreciably the rate of peritoneal absorption but would greatly increase the mass required for an equivalent osmotic effect.

During the exchange, the net osmolality of dialysate at a given time reflects the balance between influx and efflux of solutes within the peritoneal cavity. The slow rate of polymer absorption is effectively compensated by the influx of solutes into the peritoneal cavity, resulting in a stable osmolality throughout the exchange. This feature of polymer dialysis may be beneficial, since it provides a more physiological environment for the peritoneal cells and membrane than the changing osmolality associated with glucose dialysis. Long-term exposure of mesothelial cells to hypertonic solution may be detrimental.[16]

The enhanced peritoneal transport of solutes of increasing molecular size observed within the first 6 h of polymer exchange is interesting and suggests an increase in either the effective surface area or peritoneal permeability. Whether this increase is related to the glucose polymer itself or other dialysis components is uncertain. It is unlikely that the polymer has a direct effect on the membrane permeability[17] but the effect may be related to the lower osmolality of the solution. Certainly a rise in transperitoneal transport of solutes of high molecular weight in relation to lower dialysate osmolality has been reported.[18]

The long-term metabolic consequences of daily transperitoneal absorption of glucose are increasingly recognised. Although the glucose absorbed may provide a useful source of calories for some malnourished patients on CAPD, in a substantial proportion it leads to obesity and hyperlipidaemia. In addition, for a growing number of diabetic patients now maintained on CAPD, an increase in insulin requirements may even exacerbate these complications. In our study the potential calorie load based on complete metabolism of the absorbed carbohydrate suggests that glucose polymer would be associated with significantly fewer calories per ml of ultrafiltrate than glucose. The systemically absorbed glucose polymer is readily hydrolysed by circulating amylase to maltose but further metabolism may be limited by the absence of maltase activity in the human circulation.[19] Even though substantial amounts of maltase have been demonstrated in a variety of extraintestinal tissues,[20,21] the enzyme is most notably present in the kidneys.[22] In renal failure, therefore, accumulation of maltose is likely and our finding of a 7–9-fold increase in maltose levels accords with this expectation. The clearance of serum maltose appears to be negligible in the absence of dialysis but its transperitoneal removal during continuous peritoneal dialysis should ensure steady-state levels in the serum. It is important to emphasise that maltose has been detected in uraemic plasma, irrespective of the mode of dialysis.[23] Whether a moderate rise in these levels causes any long-term adverse effects remains unknown. In short-term studies, circulating maltose levels ten times the amount we observed were not associated with any adverse effects, or changes in serum glucose or insulin levels in normal or uraemic patients.[22,24,25]

At present a single daily overnight exchange of glucose polymer (10-12 h) with two to three glucose exchanges during the day may be feasible and would minimise the rise in serum maltose. If long-term studies confirm the safety of moderately raised maltose levels in uraemic circulation, glucose polymer dialysis would have the potential advantages of reducing the total number of exchanges to two or three per day in some patients and virtually obviating the need for overnight hypertonic (glucose 3·86%; 484 mOsm/kg) exchanges. Furthermore, absence of hyperglycaemia during glucose polymer dialysis would be particularly useful for diabetic patients on CAPD.

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Correspondence should be addressed to C. D. M.

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TRANSPLANTATION OF LIVER, HEART, AND LUNGS FOR PRIMARY BILIARY CIRRHOSIS AND PRIMARY PULMONARY HYPERTENSION

JOHN WALLWORK ROGER WILLIAMS[1]
R. Y. CALNE[2]

Heart Transplant Unit, Papworth Hospital, Papworth Everard, Cambridgeshire; Liver Unit, King's College Hospital, London;[1] Department of Surgery, University of Cambridge, Addenbrooke's Hospital, Cambridge[2]

Summary Liver, heart, and lung replacement was performed in a woman with severe pulmonary hypertension, cardiorespiratory failure, and end-stage primary biliary cirrhosis. The main surgical considerations were the staging of the various parts of the operation in relation to cardiopulmonary bypass and performing the recipient procedures as expeditiously as possible to reduce the bypass time to a minimum. The patient was able to leave hospital on the 46th postoperative day on low doses of immunosuppressive agents, with excellent liver and cardiopulmonary function. This early satisfactory outcome shows the feasibility and potential of the procedure: such combined allografting may be a suitable treatment in carefully selected cases of advanced liver and lung disease from other causes.

Introduction

TRANSPLANTATION of another organ together with the liver may be needed to correct congenital errors of metabolism and to replace the diseased organ, as in hypercholesterolaemia[1] and myocardial ischaemia and in primary hyperoxaluria with kidney failure.[2] In other instances both organs for transplantation have had end-stage diseases (eg, in cirrhosis with glomerulonephritis or diabetic renal failure). The pancreas has also been transplanted with the liver in a cirrhotic patient with severe diabetes.[3] In the present report liver, heart, and lungs have been transplanted simultaneously in a patient with end-stage primary biliary cirrhosis and severe pulmonary hypertension.

Case History

The patient is a woman now aged 35. Jaundice and pruritus due to primary biliary cirrhosis (PBC) developed in 1978, but she remained reasonably well until 1982 when she complained of increasing dyspnoea on exertion with occasional episodes of haemoptysis. When referred to King's College Hospital in November, 1984, she had, in addition to signs of PBC, clinical evidence of primary pulmonary hypertension and right ventricular hypertrophy. Cardiac catheterisation showed pulmonary artery and right ventricular pressures of 90/0 and 90/30 mm Hg, respectively, with normal oxygen saturation. Test doses of nifedipine and isoprenaline had no effect, and on angiography there was dilatation of the main pulmonary artery with a regular "pruning" of the peripheral vessels. Pulmonary function tests showed normal ventilatory capacity with striking reduction in transfer factor (12·1 mmol/kPa per m) compared with a predicted value of 23·8. At that time, the serum bilirubin was 190 μmol/l and mitochondrial antibody titre was 1 in 640. Anticardiolipin was negative.

She was readmitted in November, 1986, having deteriorated greatly after termination of a pregnancy in September. Whereas she had been able to get around at her own pace, she was now breathless at rest and could walk only a few yards. On examination she had right heart failure. Chest X-ray showed a 1·3 cm increase in the cardiac silhouette over the previous 12 months. Despite hyperventilation she was still hypoxic. Blood gas tests were: oxygen pressure (PO_2) 9 kPa (normal range 11–15); carbon dioxide pressure (PCO_2) 2·8 kPa (4·3–6·0); pH 7·46 (7·37–7·45); and HCO_3 15 mmol/l (22–30)—which were indicative of a mild metabolic acidosis with a compensatory respiratory alkalosis. Liver function had also deteriorated, with a serum bilirubin of 282 μmol/l; and on endoscopy there were grade III varices and a haemorrhagic gastritis.

As a result of this assessment she was accepted as a candidate for combined transplant surgery.

Donor Organs and Procurement

Selection of donor organs was based on the established criteria for separate heart-lung and liver transplantation, particularly important being evidence of good gas exchange in the donor and appropriate size of the intrathoracic organs. For this small recipient (weight 45 kg; height 1·49 m), the donor was a 14-year-old girl with brainstem destruction following a head injury sustained in a road traffic accident. She had been ventilated for 4 days. Her cardiovascular state had become unstable with periods of

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Computer simulations of ultrafiltration profiles for an icodextrin-based peritoneal fluid in CAPD

BENGT RIPPE and LARS LEVIN

Department of Nephrology, University Hospital of Lund, Lund, Sweden

Computer simulations of ultrafiltration profiles for an icodextrin-based peritoneal fluid in CAPD.

Background. The three-pore model of peritoneal transport has the ability to predict ultrafiltration (UF) profiles rather accurately, even when high molecular weight (MW) solutes are employed as osmotic agents in continuous ambulatory peritoneal dialysis (CAPD). In the present simulations, we wanted to assess, for various theoretical perturbations, the UF properties of a peritoneal dialysis (PD) solution with an osmotic agent having an average MW of 20 kD and a "number average MW" of 6.2 kD, which is similar to that of icodextrin (ICO).

Methods. For a PD solution containing a completely monodispersed 20 kD MW osmotic agent, the degree of UF modeled is much higher than that reported for ICO. Hence, to model the behavior of ICO, we subdivided the ICO molecules into eight or more different MW size fractions. For simulations using six or eight subfractions, we obtained an excellent fit of simulated to reported UF data. More dispersed solutions produced UF profiles similar to that with eight fractions.

Results. A 2.05 L 7.5% ICO PD solution, despite being slightly hypotonic, yielded a UF volume of nearly 600 mL in 12 hours, modeled for patients not previously exposed for ICO. After nine hours, the UF volume exceeded that produced by 3.86% glucose. The UF rate and volumes increased in proportion to (*1*) the ICO concentration, (*2*) the peritoneal surface area, and (*3*) the peritoneal UF coefficient, but was almost insensitive to increases in the instilled fluid volume. Simulated for patients previously exposed to ICO, having steady-state plasma concentrations of ICO degradation products, the predicted UF volume at 12 hours was reduced to approximately 400 mL.

Conclusion. Employing the three-pore model of peritoneal transport and taking into account the polydispersed nature of ICO, it was possible to accurately computer simulate the UF profiles of ICO in accordance with reported data. The simulations suggest an advantage of using ICO in patients with type I UF failure, where UF with a high-MW osmotic agent will exceed that seen in patients not showing UF failure who are on glucose-based PD solutions.

Key words: dialysate, membrane permeability, three-pore model of peritoneal transport, fluid and solute transport.

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The three-pore model of peritoneal transport has been successfully employed to predict ultrafiltration (UF) profiles in continuous ambulatory peritoneal dialysis (CAPD) in normal and a number of perturbed conditions [1, 2]. The model assumes the presence of a large number of small pores (radius 40 to 50 Å) in the peritoneal membrane, permeable to most small solutes and water, together with a very low number of large pores (radius ≈250 Å), allowing the transport of macromolecules from blood to peritoneum. A third transperitoneal exchange route is predicted to conduct water via "ultrasmall pores" in the plasmalemma of radius ≈3 to 5 Å, which rejects solute transport, denoted aquaporins [3, 4]. Aquaporins play an important role in peritoneal osmotic water transport and in solute sieving. They seem to provide an explanation for the apparent paradox that the rather "open" peritoneal membrane actually effectively "sieves" small solutes from water when UF is driven by high crystalloid (glucose) osmotic gradients [2].

Compared with traditional models, such as that described by Pyle, Moncrief, and Popovich (P&P) [5] and Vonesh et al [6], small solute reflection coefficients are approximately one order of magnitude lower and the peritoneal UF coefficient approximately tenfold higher in the three-pore model. According to the P&P model, for example, there is hardly any difference in osmotic efficiency among solutes of different sizes. However, the three-pore model seems to yield realistic estimates of small-solute reflection coefficients, which are less than 0.1, while those of larger solutes approach unity. The three-pore model thus explains why high molecular weight (MW) solutes are more efficient on a molar basis as osmotic agents in PD than small solutes [7], and it has been demonstrated to be superior to previous models in predicting UF profiles for high-MW osmotic agents [8].

The present study deals with the rather complex computer modeling of a macromolecular osmotic agent, namely, glucose polymers or dextrins, using the three-pore model of peritoneal transport [2, 9]. Icodextrin (ICO) is a polydispersed glucose polymer having a MW distribution such that 85% of the molecules have a MW between 1638 and 45000 D, and 6% less than 1638 D. The weight average MW is around 16 to 20 kD, and the number average MW is less than 6.5 kD [10–13]. Actually, a majority of the molecules in the ICO preparation have a MW of less than 3 kD. Although ICO is very polydispersed, previous attempts to theoretically analyze the clinical UF profiles for ICO have not taken its polydispersity into account [14]. In the present simulations, however, polydispersity was accounted for by subdividing the ICO molecules into eight major size fractions, which yielded UF profiles compatible with data in the literature. The aim of the present study was to simulate a number of different physiological and pathophysiological scenarios compatible with different clinical situations encountered in peritoneal dialysis, and to predict the UF profiles for ICO in these situations.

METHODS

Parameter selection

The three-pore model has been described at some length elsewhere [1, 2, 8, 9, 15]. Basically, the three-pore model conceives the capillary membrane (the endothelium) as the limiting barrier for solute and fluid transport between blood and dialysate, more or less neglecting the interstitium and any concentration gradients herein. In this work, the three-pore model was slightly modified from its original version by setting the small pore radius at 43 Å, the UF coefficient at 0.074 mL/min/mm Hg, and the fraction of the UF coefficient accounted for by the aquaporins at 0.02. All of these values were obtained from parameter optimization procedures based mainly on data from previous studies on glucose-based dialysis fluids [15, 16]. Dextrin's molecular radii (a_e) was obtained from $a_e = 0.486\ (MW)^{0.386}$ [1], and dextrin permeability-surface area products [PS or mass transfer area coefficients (MTACs)] were assessed from the theory of restricted diffusion (and convection) across membranes having cylindrical pores (pore theory), setting the "area parameter" ($A_0/\Delta X$) at 25,000 (cm) [2, 16]. Dextrin clearance out of the peritoneal cavity was set at (PS + 1.2) mL/min to account for the transcapillary clearance (PS) and the clearance to peritoneal tissues (~1.2 mL/min). Direct lymphatic clearance (0.3 mL/min) was added separately [1]. The simulations were performed assuming that the patients had not been previously exposed to ICO, except in one case, in which we also tried to model a situation relevant to that during long-term use of ICO. The parameters used for the computer simulations are shown in Table 1. The major equations employed and the calculation techniques applied are found in the **Appendix**. A fourth- to fifth-order Runge-Kutta algorithm (Maple V software) was employed to carry out the integrations of the differential equations, describing the osmotic flow across each of the three subsets of membrane pores in order to produce the simulated UF profiles.

Table 1. Parameters used for computer simulations of intraperitoneal volume versus time [V(t)] curves according to a three-pore model of membrane selectivity

Small pore radius (r_s) *Å*	43
Large pore radius (r_L) *Å*	250
Fractional small pore UF coefficient (α_s)	0.900
Fractional transcellular UF coefficient (α_c)	0.020
Fractional large pore UF coefficient (α_L)	0.080
Ultrafiltration coefficient (L_pS) *mL/min/mm Hg*	0.074
Osmotic conductance to glucose ($L_pS\ \sigma_g$) *µL/min/mm Hg*	3.6
"Unrestricted" pore area over unit diffusion distance for small pores ($A_0/\Delta X$), cm	25,000
PS ("MTAC") for glucose *mL/min*	15.4
PS ("MTAC") for "Na" and "an" *mL/min*	6.0
Peritoneal lymph flow (L) *mL/min*	0.3
Transperitoneal hydrostatic pressure gradient (ΔP) *mm Hg*	8
Transperitoneal oncotic pressure gradient ($\Delta\pi_{prot}$) *mm Hg*	22
Dialysis fluid volume instilled *mL*	2050
Peritoneal residual volume (V_r) *mL*	300
Serum urea concentration *mmol/L*	20
Serum sodium (and sodium associated "anion" concentration) *mmol/L*	140
Serum glucose concentration *mmol/L*	6.5
Dissociation factor for "Na" and "an"	0.93

Mass and osmolality spectrum of ICO

Icodextrin is a polydispersed preparation, with 5 to 6% of the mass spectrum in the 0.18 to 1.6 kD MW range and 8 to 9% of the mass spectrum above 45 kD in MW [10]. Approximately 80% of the mass, however, is represented by molecules having MWs ranging from 10 to 30 kD. An attempt to mimic this spectrum, a procedure using eight subfractions of ICO, was used in this study. This is shown in Figure 1A, where the percentage of total osmolality or total preparation weight in each of the fractions is plotted versus log MW. This spectrum should be rather close to that used in commercial preparations of ICO [10–12]. Note that the osmolality spectrum, which determines the osmotic behavior of the solution, is completely different from the mass spectrum. While nearly 90% of the mass is provided by molecules larger than 9 kD in MW, these MW fractions account for less than 30% of the total osmolality of the preparation, as the osmolality is based on the number of molecules. The "effective" osmolality of this solution is, however, based on the osmolality of each fraction times the corresponding lumped reflection coefficient in the three sets of membrane pores. In Figure 1B, this spectrum (% of total), that is, osmolality times the lumped σ for each fraction, is presented. Figure 1 underscores the importance of the larger size fractions as being more efficient osmolytes when compared with the smaller size fractions.

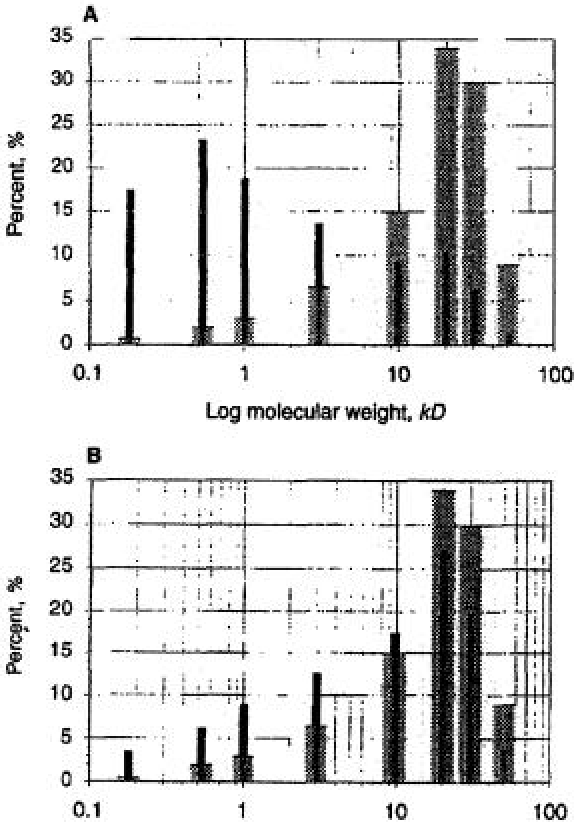


Fig. 1. (*A*) **Mass and osmolality spectra of icodextrin.** The osmolality spectrum (■), which critically determines the osmotic behavior of the solution, is completely different from the mass spectrum (■). Whereas nearly 90% of the mass is provided by molecules larger than 9 kD in molecular weight (MW), these MW fractions represent less than 30% of the total osmolality of the dextrin preparation. (*B*) Mass spectrum and spectrum of "effective" osmolality of icodextrin. The "effective" osmolality spectrum (■), although prominent for the low MW fractions, largely follows the mass spectrum (■).

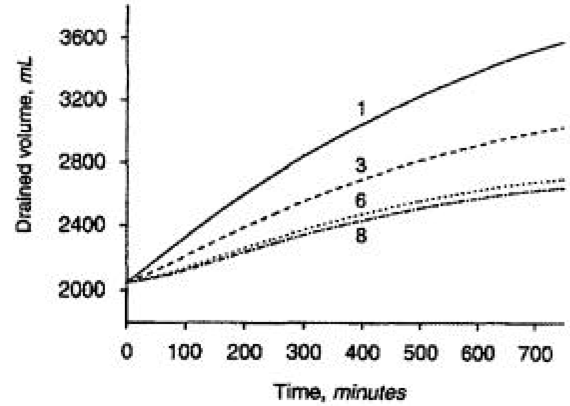


Fig. 2. Computer-simulated ultrafiltration (UF) profiles for 7.5% monodispersed 20 kD dextrin solution (denoted "1") in comparison with the icodextrin having the composition depicted in Figure 1, with eight major MW fractions (denoted "8"). Two preparations of intermediate "dispersion" are also shown. There is almost no difference between the UF profile simulated for six versus eight subfractions of the icodextrin preparations. The two lower curves seem to fit well with literature.

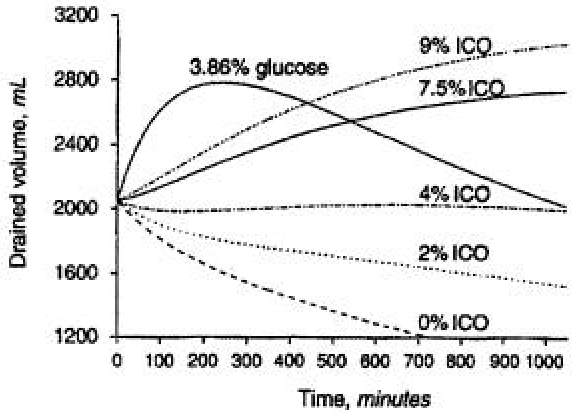


Fig. 3. Computer-simulated UF profiles for five different icodextrin concentrations (0 to 9% ICO) compared with that simulated for 3.86% glucose (G). The 4% ICO preparation seemed to be largely isovolumetric during 12 hours. After eight to nine hours, the UF volume for 7.5% icodextrin (polydispersed, 8 fractions) exceeded that for 3.86% glucose.

RESULTS

Impact of molecular size dispersion on the osmotic behavior of dextrin preparations

Figure 2 shows the simulated UF profiles for a 7.5% homogeneous 20 kD dextrin solution in comparison to an ICO solution with the composition depicted in Figure 1, having eight major MW fractions. Two preparations of intermediate dispersion are also shown. Note the small difference between the curves simulated using 6 versus 8 subfractions of the ICO preparation. The two lower curves seem to fit well the UF data reported in the literature for ICO [11–14]. Actually, the more dispersed solutions produced UF profiles similar to that simulated using only eight fractions (data not shown), that is, coinciding with the lower curve. In the next sections, computer simulations mainly based on the eight subfractions are presented.

Simulated UF profiles at various concentrations of ICO in previously unexposed patients

Figure 3 shows the computer-simulated UF profiles for five different ICO concentrations (0 to 9% ICO) compared with that simulated for 3.86% glucose [2]. Simulations were made using eight ICO subfractions (compare with Fig. 1), and the dwell time was extended to 17 hours (1020 min). A 7.5% ICO preparation seemed to yield a UF volume that was higher than that obtained

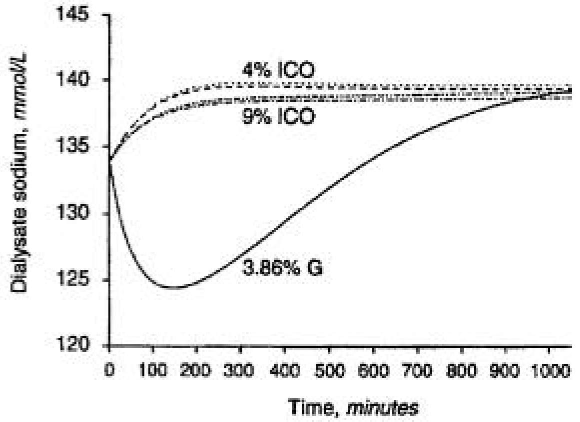


Fig. 4. Sodium sieving profiles for icodextrin (ICO) and 3.86% glucose (G). There is a near absence of sodium sieving for icodextrin (4% and 9%), whether given as a homogenous preparation (lower curve in each pair of curves), yielding a high degree of UF, or as a polydispersed solution (8 subfractions; upper curve in each pair denotes 4% ICO and 9% ICO). Sodium sieving for 3.86% glucose (G, lower solid line) is simulated for comparison.

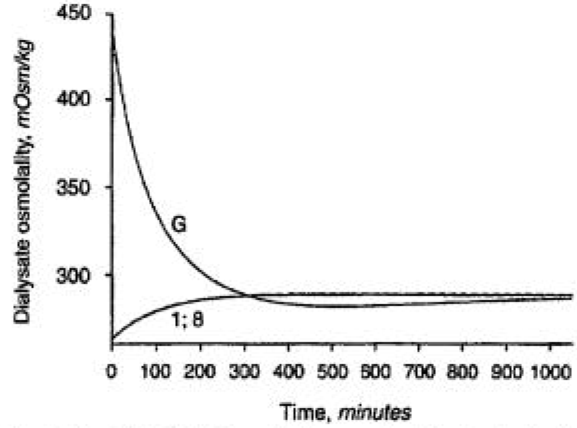


Fig. 5. Simulated dialysate osmolality versus dwell time for icodextrin (ICO, dashed line) and for 3.86% glucose (G, solid line) during a single dwell. Note that the ICO solution (whether homogeneous, "1", or polydispersed, "8") is simulated to be hypotonic during the first four to five hours of the dwell, in stark contrast to the situation for 3.86% G.

for 3.86% glucose after nine hours (≈500 mL). A 4% ICO preparation, however, seemed to be largely "isovolumetric" during 12 hours.

Sodium sieving profiles for ICO and for 3.86% glucose

Figure 4 demonstrates the near absence of sodium sieving for ICO whether given as a homogeneous preparation (lower curve in each pair of dextrin curves) for 4 and 9% ICO or as a polydispersed solution (8 subfractions; the upper curve in each pair). By contrast, the marked sodium sieving occurring for 3.86% glucose resulted from osmotic water flow through the aquaporins. Still, the fact that 9% ICO showed slightly lower dialysate sodium than 4% ICO indicates that the sodium sieving was not completely abolished even for ICO-based dialysis fluids.

Osmolality profiles for ICO and for 3.86% glucose during a single dwell

Figure 5 depicts dialysate osmolality as a function of dwell time for glucose and monodispersed (20 kD/fraction) ICO or polydispersed (8 fractions) ICO. The ICO solution was slightly hypotonic to plasma (plasma osmolality ≈290 mOsm/kg) during the first four to five hours of the dwell, in stark contrast to the situation for 3.86% glucose. This is due to the "colloidal" nature of ICO in comparison to any low MW osmotic agent.

Simulated UF profiles for 7.5% ICO in patients with steady-state plasma levels of ICO and its metabolites

In the present simulations, we preferred to show the UF profile data for patients previously unexposed to ICO.

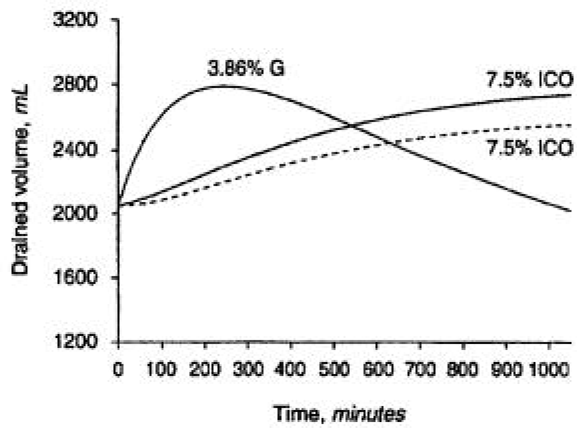


Fig. 6. Computed UF profiles for 7.5% icodextrin (ICO) in patients with long-term exposure to ICO (lower, dashed line curve) in comparison with patients exposed to 7.5% ICO for the first time. Simulations of plasma concentrations of ICO and ICO degradation products in the long-term patient were based on data from Davies and Posthuma et al [10, 17].

It should be noted, however, that patients with steady-state plasma levels of ICO and its metabolites following long-term ICO use showed significantly lower UF profiles than the previously unexposed patients, as illustrated in the simulation shown in Figure 6. For this simulation, published data were used and rearranged to fit the present model [10, 17]. Corresponding to the different size fractions, the following plasma ICO metabolite concentrations were used (the plasma glucose concentration is given in Table 1): 0.54 kD, 1.5 g/L; 1.0 kD, 1.3 g/L; 3.0 kD, 0.8 g/L; 10 kD, 0.6 g/L; and 20 kD, 0.4 g/L. Note that the UF volume in 17 hours was reduced from 670 to

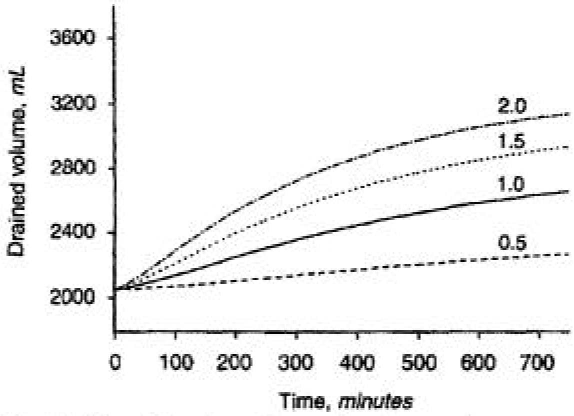


Fig. 7. Effects of alterations of the vascular surface area (area parameter, $A_0/\Delta X$) on UF profiles for 7.5% icodextrin. The surface area is varied from 50% of control (0.5) to twice the control value (2.0). Control curve is denoted by "1.0" (solid line). Note the marked increase in UF obtained when surface area is increased.

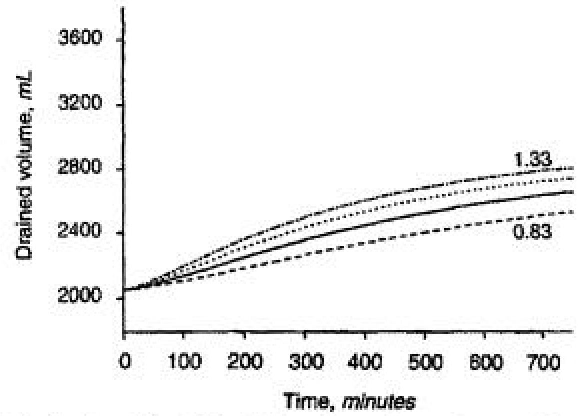


Fig. 8. A special condition of changes in vascular surface area, where for any step change in surface area (S), the permeability-surface area [PS; mass transfer area coefficient (MTAC)] is altered in proportion to S, but the peritoneal UF-coefficient (L_pS) is only altered by one third (33%). The solid line symbolizes control situation (PS and LpS at control values). The dotted line depicts a situation in which PS is altered to 150% and LpS to 117% of control. Thus, if PS is doubled, L_pS is increased by 33% (denoted "1.33"), and when PS is reduced by 50%, L_pS is reduced to 83% of control value (denoted "0.83").

500 mL in the long-term patients. Furthermore, the UF volume at 12 hours in the long-term patients could be expected to be only 410 mL instead of 580 mL, and the time at which the UF volume for 7.5% ICO exceeded that of 3.86% glucose was 11 hours instead of 9 hours after long-term ICO treatment. In the following simulations, however, only the situation in patients who had not been previously exposed to dextrins is discussed.

Effects of alterations of vascular surface area on the UF profile of 7.5% ICO

Figure 7 demonstrates the computer-simulated change in UF profiles for 7.5% ICO that occurred when the (vascular) surface area ("area parameter"; $A_0/\Delta X$) varied from 50% of control (0.5) to twice the control value (2.0). Note the marked increase in UF obtained when the surface area was increased. By contrast, for 3.86% glucose, there was a reduction in UF after 200 minutes when the capillary surface area was increased (compare with Fig. 5 in [2]). This pattern of alterations is expected to occur in, for example, peritonitis, where ICO would be superior to glucose as an osmotic agent.

Effects of varying solute diffusion capacity more than the peritoneal UF coefficient

The scenario of simultaneous increases in PS and L_pS, where the increase in L_pS is less prominent than predicted from the changes in surface area (S) is common in so-called type-1 UF failure [18, 19]. Figure 8 depicts a condition in which for any step change in the surface area, PS (MTAC) was altered in proportion to S, but L_pS was only altered by one third. Thus, if PS was doubled, L_pS increased only by 33%. Again, although less pronounced than in Figure 6, ICO produced an improved

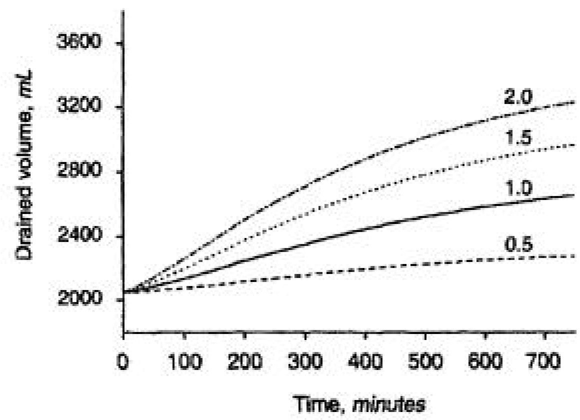
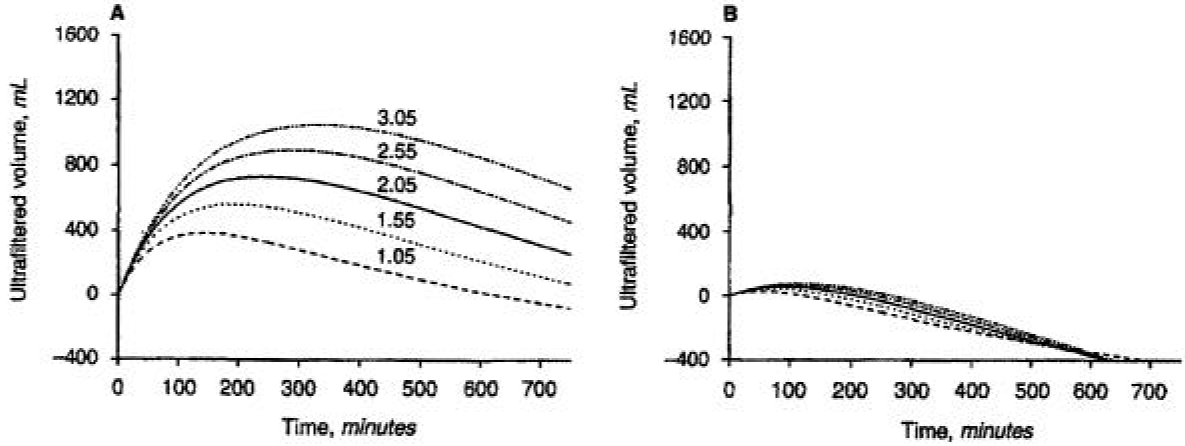


Fig. 9. Effects of varying the peritoneal UF coefficient (L_pS), but not the solute diffusion capacity (PS or MTAC) on UF profiles for 7.5% ICO. L_pS is varied from 50% of control ("0.5") to 100% above control ("2.0"), keeping the PS for small solutes constant. In this situation, there is a marked increase in UF transport with ICO. With G, the maximum UF volume after approximately 200 minutes is also increased with increasing L_pS.

UF profile compared with control when the (vascular) surface area was increased.

Effects of varying the UF coefficient on the UF profiles for 7.5% ICO

When G was used as osmotic agent, increases in L_pS caused increases in both the initial UF and in reabsorption of fluid from the peritoneal cavity to plasma after four hours of the dwell [2]. The "height" of the UF



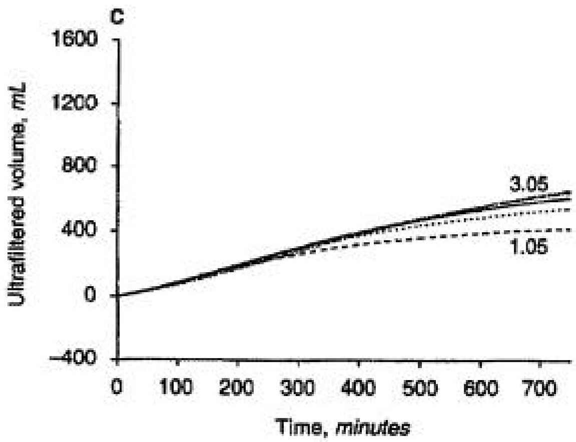


Fig. 10. Effects of varying the instilled volume on the UF profiles for 3.86% (*A*) and 1.36% glucose (*B*). The instilled volume seems to have a major impact on the UF profiles produced by 3.86% glucose (G), but not on those for 1.36% G. (*C*) Effects of varying the instilled volume on the UF profiles for 7.5% ICO. During the first 300 minutes, there is hardly any change in UF profile for increases in instilled volume. However, after 300 minutes, there is a slight correlation between instilled volume and UF volume, especially for 1.05, 1.55, and 2.05 L of instilled volume (lower three curves). However, 2.55 and 3.05 L of instilled volume (upper two curves) yield approximately similar UF profiles over 12 hours.

curve, but not the time to the curve peak (t_{peak}), increased markedly for increases in L_pS (compare with Fig. 6 in [2]). For ICO, there was also a marked, more or less proportional, increase in UF volume after 10 hours when L_pS was increased, as demonstrated in Figure 9, where L_pS varied from 0.5 of control to twice the control.

Effects of varying the instilled volume on the UF profiles for 7.5% ICO and for glucose

While the instilled volume apparently had a major impact on the UF profile produced by 3.86% glucose (Fig. 10A) [2], but not for 1.36% glucose (Fig. 10B), it only had a marginal effect on the UF profiles caused by 7.5% ICO (or 4% ICO; data not shown), as depicted in Figure 10C. In Figure 10, the instilled volume varied from 1.05 L (in 0.5 L steps) to 3.05 L and simulated versus UF volume. Note that 2.55 and 3.05 L of instilled ICO volumes yielded nearly identical UF profiles. A markedly increased UF volume is thus not to be expected from an increase in instilled ICO volume.

Effects of an increased direct lymphatic absorption on UF profiles for 7.5% ICO

When a high MW solute is placed in the peritoneal cavity, it will disappear by direct lymphatic absorption (L), by tissue absorption, and by varying degrees of capillary absorption. The direct peritoneal to plasma absorption of a large solute usually represents only a small fraction of the total disappearance of the solute. The tissue absorption of ICO in this study was set at 1.2 mL/min, which largely accounted for the discrepancy between total large solute clearance out of the peritoneal cavity and its "direct" lymphatic absorption (L) [20, 21]. Figure 11 shows how variations in direct lymphatic absorption affected the UF profile for 7.5% ICO. When L is 1.0, there was hardly any UF at all. For higher values of L, UF became negative. It has to be pointed out that, indeed, very high values of L are extremely uncommon clinically [21].

Effects of combining ICO with glucose

Figure 12A shows UF profiles for 7.5 and 4% ICO solutions, which also contained 1.36% glucose. An ICO

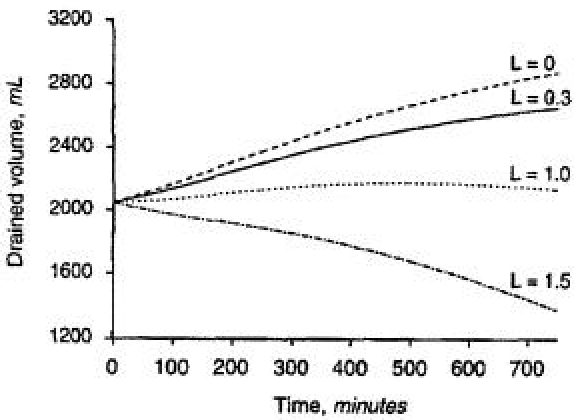


Fig. 11. Drained volume versus time curves for 7.5% ICO obtained at variations of the direct lymphatic absorption (L). The UF profile is largely "isovolumetric" for L = 1.0 (mL/min), but becomes negative for higher values of direct lymphatic absorption.

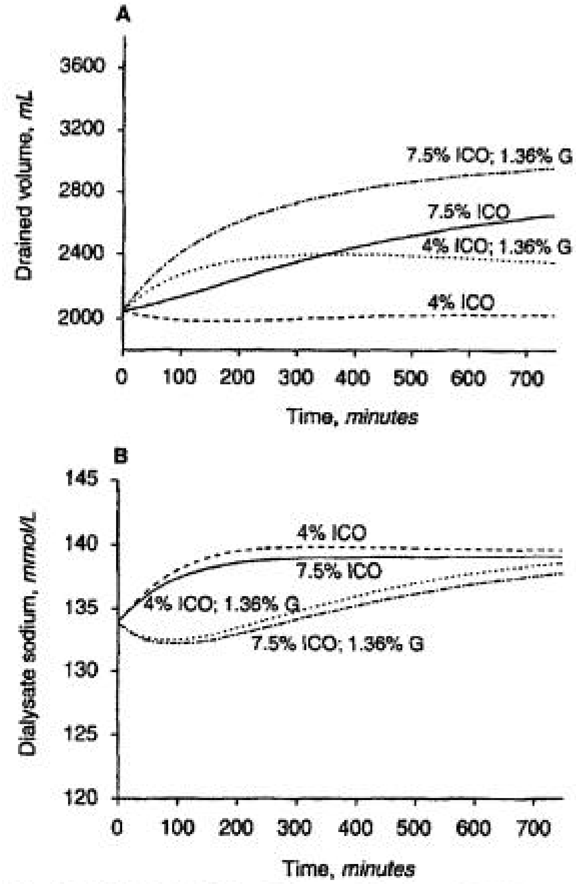


Fig. 12. (*A*) Simulated UF profiles for combinations of 1.36% G with 4% (dotted line) or 7.5% (solid line) ICO solutions. Note that the presence of low MW osmotic agents (G) initially yields a significant UF. The presence of ICO will maintain the UF rate more or less constant following the first 300 minutes of the dwells. (*B*) Sodium sieving curves corresponding to the curves in Figure 10A. Note that only the G containing dialysis fluid causes significant sodium sieving.

of 7.5% and 4% are shown for comparison. Glucose actually produced a marked initial UF and ICO maintained this UF level during the 12-hour dwell. Even a 4% ICO solution yielded a favorable UF volume at 10 to 12 hours. Figure 12B shows the dialysate Na as a function of dwell time for the curves shown in Figure 12A. Because of the presence of rather high concentrations of a low MW osmotic agent (glucose), the Dex/glucose solutions caused significant sodium sieving, unlike the pure Dex solutions, which produced weak, or absent, reductions in dialysate sodium.

DISCUSSION

To correctly computer simulate the osmotic behavior of ICO, it is necessary to consider its polydispersed nature. Actually, the difference in osmotic behavior between a homogenous dextrin having a MW of 20 kD and a polydispersed dextrin with a weight average MW of 20 kD and a number average MW of approximately 6 kD [10] is very pronounced. Taking into consideration the polydispersity of ICO, it could be shown, however, that it is sufficient to subdivide the dextrin molecules into six to eight different MW (or size) fractions. Further subdividing the osmotic molecules into more fractions did not produce any further changes in UF profiles compared with that generated with only eight fractions. In the present simulations, however, we did not take into account any degradation of high MW dextrins into low MW dextrins, as proposed from rat experiments [22]. It should be pointed out that even when completely undegraded, the majority of osmotically active dextrin molecules (≈70%) are in the low MW range (<3 kD), despite the fact that most of the molecular mass (80%) is provided by molecules in the high-MW mass range. Still, since the solute osmotic efficiency will increase with increases in molecular size, the UF contribution of the different molecular size fractions, although more pronounced for the low MW solutes, will be largely in proportion to the molecular mass spectrum.

According to the present simulations and in agreement with the study by Ho-dac-Pannekeet et al in humans [14], ICO remained hypotonic compared with plasma during the first two hours of the dwell. Furthermore, the rate of net UF was initially quite low, but increased slightly over the first to second hours of the dwell in order to remain steadily increased for up to 10 hours of the dwell. Indeed, the UF volume did not reach a maximum during the first 12 hours after fluid instillation. The reason for the initial slight depression of UF rate was the initial crystalloid osmotic imbalance between plasma and dialysate, particularly concerning the concentrations of urea and glucose, which were initially near zero in the dialysate but high in plasma (especially for urea). This is evident from computer simulations in which glucose, sodium, and urea concentration gradients across the peritoneum were set at zero (data not shown). Normally, these crystalloid (small solute) osmotic pressures gradually dissipate over the first two to three hours of the dwell, particularly when urea has equilibrated across the peritoneum. In animal studies, the contribution of initial degradation of large MW dextrins into low MW dextrins and the fact that the osmolytes have to diffuse to the capillary walls to exert their effect (discussed later in this article) may also contribute to an increasing osmotic capacity of the dialysis fluid developing with increasing dwell time [22].

Overall, the general UF behavior of the simulated 7.5% ICO solution is in accordance with previously published data. In the MIDAS study, the long-term patients (5 months) produced a UF volume of 510 ± 260 ($\pm$ SD) mL at 8 hours and of 550 ± 240 mL at 12 hours [11–13]. Previously unexposed patients, in accordance with the present simulations, produced a higher UF volume: 710 ± 350 mL in eight hours. In the present simulations, 7.5% ICO produced the same cumulative amount of net UF as 3.86% glucose at nine hours in previously unexposed patients. In patients showing steady-state plasma levels of ICO and its metabolites, this occurred at ~11 hours. The present simulations are also in rough agreement with measured and extrapolated values from more detailed dwell studies in humans [14], where the degree of sodium sieving was also studied. In agreement with the present results, the dialysate to plasma concentration ratio (D/P) for sodium remained more or less a constant over time during the first few hours of the dwell; that is, no significant sodium sieving was observed with ICO [14]. In another recent study of automatic PD (APD) patients [23], "daytime" UF volume with 7.5% ICO during 12 months of follow-up was only 204 ± 95 mL ($\pm$ SEM), which is lower than simulated in our study and much lower than indicated from the MIDAS study or the dwell study of Ho-dac-Pannekeet et al [14]. The reason for this discrepancy is not known. Generally, however, there is a lack of data on the UF properties of ICO during long dwells, and it is speculated that the data of Posthuma et al may be representative of a cohort of patients showing relatively low values of the peritoneal UF coefficient (L_pS; discussed later in this article) [17].

Ultrafiltration failure (UFF) is a frequent complication of long-term CAPD. In six years, the risk of developing UFF is approximately 30% [18]. The most frequent cause of UFF is probably an increased effective vascular surface area (increased $A_0/\Delta X$) [18, 19]. The present simulations clearly show an advantage of using ICO in patients with this condition [25]. Thus, in contrast to the situation when glucose is used as an osmotic agent, ICO will actually produce an enhanced UF rate when the vascular surface area is increased. A doubling of the effective vascular surface area implies a near doubling of the UF volume with ICO (from ~580 to 1100 mL) at 12 hours in patients who were not previously exposed to ICO. This increase in UF occurs under the provision that both L_pS and PS will increase as a result of the enhanced vascular surface area. To the extent that L_pS is increased less than the increase in PS, when vascular surface area is increased, the improvement in UF profile with ICO will be less pronounced [26]. Anyway, it can be predicted that most UFF patients will actually improve their UF during ICO dwells compared with non-UFF patients. It should be noted, however, that in the rare cases when the UFF depends on a high "direct" lymphatic absorption rate (L), there would hardly be an advantage of using ICO, as demonstrated in the present simulations.

For patients classified as "high" or "high average" transporters according to the peritoneal equilibration test (PET) [27], a similar reasoning as for the UFF patient applies. It is probable that a high or high average transporter has a higher effective vascular surface area than the "low" or "low average" transporter. Again, to the extent that the vascular surface area, and hence L_pS, is increased in the high average transporters [26], they will show an improved UF response as compared with low or low average transporters.

Whereas the instilled volume was of great importance in determining the UF profiles for hypertonic glucose [2, 24], the impact of the instilled volume on UF with 7.5% ICO was rather marginal. Actually, during the first five hours of the dwell, the UF profiles looked almost exactly the same whether the instilled volume was 1.05 or 3.05 L. However, between 5 and 12 hours, there was some separation of the curves, implying some improvement of UF volume for the higher instilled volumes. However, all in all, there is no major rationale for increasing the instilled volume to improve UF with ICO. The negligible impact of instilled volume on UF volume for 1.36% glucose is a bit surprising, but fits very well with recent data in rats [24]. Indeed, in that animal study, increases in instilled volume produced improved UF for 3.86% glucose in accordance with previous simulations [2]. However, for 1.36% glucose, increases in instilled volume tended to impair the UF capacity. In the present simulations, such an impairment seemed to occur after 500 minutes of dwell time. This phenomenon would have been even more marked, however, if intraperitoneal hydrostatic pressure (IPP) had been simulated to increase in a more exaggerated fashion as a function of intraperitoneal volume (compare with Eq. 2, **Appendix**) than in the present study. The slight discrepancy between the computer simulations and the above-mentioned UF data in rats can thus be readily explained.

Combining low concentrations of glucose (for example, 1.36% glucose) with 7.5% ICO will produce a marked initial UF, usually followed by a steady UF rate over time, resulting in more than 800 mL of UF volume in 12 hours for the mentioned ICO/glucose formulation. Also, 4% dextrin together with 1.36% glucose will result in approximately 300 mL of UF volume in 10 to 12 hours. In a recent study in rats, the addition of low concentrations of glucose to ICO did not seem to markedly improve UF in a four-hour dwell, but did improve it in two hours [24]. It should be noted, however, that the fluid kinetics in a rat is markedly different from that in humans in that the UF profiles are "compressed" in time by a factor of 2 to 3 in rats. Furthermore, in the mentioned rat study, there were indications of degradation of high MW dextrins into low MW dextrins, which were not considered in the present simulations. This may account for the observed differences.

The general validity and applicability of the three-pore model of peritoneal transport has been discussed at some length elsewhere [1, 2, 8, 9, 15], but some additional aspects with particular relevance to the situation of employing macromolecules as osmotic agents should be considered here. In particular, in the mentioned study of rats, there was an initial delay in UF after the instillation of the ICO containing dialysis fluid [24]. Part of this initially reduced UF is obviously due to the presence of initial crystalloid osmotic imbalances between in plasma and dialysate, as discussed previously in our article. Part of the delay may also be due to the fact that the capillary membrane (endothelium) is not in direct contact with the dialysate, but instead is distributed within the matrix of the interstitium. In such a distributed model [28, 29], there may be a significant interstitial diffusion resistance to large solutes, producing a delay in the establishment of a full osmotic force across the endothelium. Furthermore, in a distributed model of peritoneal transport, any changes in the anatomical endothelial surface area will not produce directly proportionate changes in overall solute transport. For example, a doubling of the endothelial surface area would theoretically result in only an approximately 45% increase of overall transperitoneal diffusion capacity [28]. In the present study, such effects were not accounted for, and the term "surface area" was used in the sense of it being "effective" vascular surface area. Despite the fact that the three-pore model does not account for the impact of the interstitial matrix on transport, it is intriguing to note that the predictions obtained using a simple "membrane model" seem to be in good agreement with the reported data, as discussed previously in this article. The error of not taking into account the impact of transport resistances in the interstitium may thus, after all, be rather minor.

In summary, the polydispersed nature of ICO has to be taken into account in computer simulations of UF profiles induced by ICO dwells. In long-term patients, the accumulation of ICO and ICO metabolites in plasma also significantly impacts on the simulated UF profiles. By applying the three-pore model of peritoneal transport, we obtained UF profiles that were remarkably similar to those reported in the literature. Furthermore, it was possible to make a number of generalizations based on the simulations. The major implication of our simulations is that UFF, when caused by increases in both small solute permeability-surface area (MTAC) and membrane UF coefficient, has a clearly positive influence on UF rate and UF volumes when 7.5% ICO is used as the osmotic agent. However, changes in instilled fluid volume will only marginally affect the UF profile when ICO is used as osmotic agent in peritoneal dialysis.

ACKNOWLEDGMENTS

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Reprint requests to Dr. Bengt Rippe, Department of Nephrology, University of Lund, S-221 85 Lund, Sweden.

APPENDIX

According to the three-pore model [1, 2], the changes in peritoneal volume (V_D) with time can be described by the following:

$$\frac{dV_D}{dt} = J_{V_C} + J_{V_S} + J_{V_L} - L \qquad \text{(Eq. 1)}$$

where J_{V_C}, J_{V_S}, and J_{V_L} represent the fluid flows through transcellular, small pores, and large pores, respectively, and L stands for the peritoneal lymph flow, which is fixed here to 0.3 mL/min. Each of the fluid flows is given by [2]:

$$J_{V_{pore}} = \alpha_{pore} L_pS[\Delta P(V_D) - \sum_{solute} \sigma_{pore,solute} \Delta\pi_{solute}(t)] \qquad \text{(Eq. 2)}$$

where α_{pore} stands for the "fraction of L_pS" accounted for by the specific set of pore; L_pS is the membrane UF-coefficient; and ΔP represents the hydrostatic pressure difference between the blood capillaries and the peritoneal cavity, which is calculated according to [30]:

$$\Delta P(V_D) = \Delta P(2050 + V_r) - \frac{V_D(t) - (2050 + V_r)}{490} \qquad \text{(Eq. 3)}$$

where V_r is the peritoneal residual volume (300 mL). In equation 2, the sum is taken for all of the solutes. The solutes used in this study are glucose, urea, eight fractions of icodextrin, plasma proteins, sodium (Na^+), and its anions. The last two crystalloid osmotic transients were treated numerically as twice the sodium osmotic transient multiplied by a dissociation factor (0.93). The symbol σ represents the osmotic reflection coefficient, calculated by [31]:

$$\sigma_{pore,solute} = 1 - \frac{(1-\lambda)^2[2-(1-\lambda)^2](1-\lambda/3)}{1-\lambda/3+2/3\lambda^2} \qquad \text{(Eq. 4)}$$

where λ is the solute radius (α_s) over pore radius (r_{pore}). According to van't Hoff's law, the ideal crystalloid osmotic gradients (in mm Hg), Δ, acting across the peritoneal membrane, are calculated from:

$$\Delta\pi_{solute}(t) = RT[C_{P,solute} - C_{D,solute}(t)] \qquad \text{(Eq. 5)}$$

where RT (the product of the gas constant and the temperatures in degrees Kelvin) is 19.3 mm Hg/mmol/L; C_P is the plasma solute concentration; and $C_D(t)$ is the concentration of solute in the dialysate as a function of dwell time. For plasma proteins, the $\Delta\pi$ was set constant at 22 mm Hg during the dwell. The changes of the mass (m) of a solute versus time (mmol/min) in the peritoneal cavity can be described by:

$$\frac{dm_{solute}}{dt} = J_{S_{S,solute}} + J_{S_{L,solute}} - \frac{LC_{D,solute}(t)}{1000} \quad \text{(Eq. 7)}$$

where L is the peritoneal lymph flow; $C_D(t)$ is the dialysate concentration of solute; $J_{S_{S,solute}}$ is the solute flux through small pores and $J_{S_{L,solute}}$ through the large pores. A "1000" in the denominator of the third term to the right is a conversion factor for L (from mL/min to L/min). Each of the solute fluxes is given by:

$$J_{S_{pore,solute}} = \frac{J_{V_{pore}}(1 - \sigma_{pore,solute})}{1000} \frac{(C_{P,solute} - C_{D,solute}(t) \cdot e^{-Pe_{pore,solute}})}{(1 - e^{-Pe_{pore,solute}})} \quad \text{(Eq. 8)}$$

Pe in Equation 8 is a modified Peclet number, defined by:

$$Pe_{solute,pore} = J_{V_{pore}} \frac{(1 - \sigma_{pore,solute})}{PS_{solute,pore}} \quad \text{(Eq. 9)}$$

where the permeability surface area (PS; mL/min), unless otherwise stated in Table 1, is defined by:

$$PS_{solute,pore} = D_{solute}\left(\frac{A_0}{\Delta x}\right)_{pore}\left(\frac{A}{A_0}\right)_{solute,pore} 60 \quad \text{(Eq. 10)}$$

Here $A_0/\Delta X$ is the "unrestricted" pore area over diffusion path length, and D_{solute} represents the free solute diffusion coefficient (in cm^2/s). A/A_0 in equation 10 represents a factor determining the degree of restricted to free diffusion occurring across the permeable pathways under study. According to pore theory, A/A_0 is a function of solute radius over pore radius, denoted λ. We have employed the following relationship to describe this parameter [31]:

$$\left(\frac{A}{A_0}\right)_{solute,pore} = \frac{(1 - \lambda)^{4.5}}{1 - 0.3956\lambda + 1.0616\lambda^2} \quad \text{(Eq. 11)}$$

For transport in the peritoneal-to-plasma direction, 1.2 mL/min (to account for tissue absorption of dextrins) was added to the otherwise calculated PS values. The PS for glucose, Na and anions were, however, set prefixed according to Table 1 (provided that surface area "S" was kept unchanged). The alterations in $C_D(t)$ with time were obtained from simple mass considerations:

$$\frac{dm_{solute}}{dt} = \frac{d(C_{D,solute}V_D)}{dt} = \frac{dC_{D,solute}}{dt}V_D + C_{D,solute}\frac{dV_D}{dt} \quad \text{(Eq. 12)}$$

from with we can extract the relationship:

$$\frac{dC_{D,solute}}{dt} = \frac{1}{V_D}\left[\frac{dm_{solute}}{dt} - C_{D,solute}\frac{dV_{D,solute}}{dt}\right] \quad \text{(Eq. 13)}$$

The sets of equations that need to be integrated numerically are the volume versus time function and all of the solute concentrations versus time. In order to calculate the initial concentrations, the following equation was used:

$$C_{D,solute}(0) = \frac{V_i C_{i,solute} + V_r C_{r,solute}}{V_i + V_r} \quad \text{(Eq. 15)}$$

where V_i is the volume of the dialysis fluid, prior to instillation, C_i the dialysis fluid solute concentration in the bag, V_r the residual volume, and C_r is the solute concentration in the residual volume. This was set equal to the plasma concentration. The initial volume was:

$$V_D = V_i + V_r \quad \text{(Eq. 16)}$$

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KINETICS OF ICODEXTRIN

Donald S. Davies

Royal Postgraduate Medical School, London, U.K.

Icodextrin is an α-1,4 linked glucose polymer produced by hydrolysis of starch and membrane fractionation to obtain material with the desired molecular weight distribution. Icodextrin is similar in structure to physiological carbohydrates such as glycogen, but the latter has a higher degree of cross-linking through α-1,6 bonds. Icodextrin is a substrate for plasma α-amylase which hydrolyzes it to maltose, maltotriose, and maltotetrose.

The fate of icodextrin administered in solution into the peritoneal cavity of patients in renal failure is determined by its stability in the peritoneal fluid, the extent of absorption, probably via the lymphatics, into the systemic circulation, and the rate of hydrolysis by plasma amylase. Early studies on a glucose polymer very similar to icodextrin demonstrated that the compounds are stable in peritoneal fluid from continuous ambulatory peritoneal dialysis (CAPD) patients, but rapidly hydrolyzed by plasma. Absorption of polymer from the peritoneal cavity was approximately 28% during a 12-hour dwell. In these studies it was apparent that hydrolysis products of up to four glucose units readily passed from the blood to the dialysis fluid, but higher molecular weight fragments were excluded.

In the MIDAS study in which patients were treated with a single daily exchange of 2 L of 7.5% icodextrin, plasma samples were obtained during visit 2 (pretreatment with icodextrin), visit 6 (1 month after commencement of treatment), visit 9 (3 months), and visit 12 (6 months) and analyzed for icodextrin and metabolites. Steady-state plasma levels of icodextrin of approximately 4.6 mg/mL and maltose of 1.1 mg/mL were stable at 1, 3, and 6 months.

During special studies, when the dwell time for icodextrin and the comparator glucose solutions were controlled to 8 or 12 hours, dialysate was analyzed for polymer and metabolites. Total carbohydrate lost from the dialysate was approximately 19.6% after 8 hours and 33.5% after 12 hours. This compares with a mean of 85.6% of absorbed carbohydrate in 7 patients treated with strong glucose (6 on 3.86%, 1 on 2.27% glucose) for 8 hours.

Plasma levels of icodextrin and maltose were measured in 12 patients who stopped once-a-day treatment with the polymer after approximately 2 years. Icodextrin (4.8 mg/mL) and maltose (1.1 mg/mL) fell to pretreatment levels in 7 – 10 days. On recommencement of treatment with polymer, plasma levels rose to steady-state levels of 4.7 mg/mL for icodextrin and 1.1 mg/mL for maltose in 7 – 10 days.

Icodextrin in solution in the peritoneal cavity is absorbed into the blood stream, probably via the lymphatic system. The extent of absorption depends on the dwell time of the solution; about 20% of total carbohydrate is absorbed in 8 hours, and this rises to 34% at 12 hours. There is no evidence of metabolism of glucose polymers like icodextrin in the peritoneal cavity. Icodextrin in the systemic circulation is hydrolyzed, probably by plasma and tissue α-amylase, to oligosaccharides, such as maltose, maltotriose and maltotetrose. These may be further metabolized, eliminated by peritoneal dialysis, or, if the patient has residual renal function, excreted in urine. The rapid attainment of steady-state plasma levels of icodextrin and its metabolites and the rapid decline when treatment is stopped is strong evidence against extensive tissue storage of the polymer.

KEY WORDS: Maltose; kinetics; α-amylase.

Icodextrin, a polydispersed glucose polymer derived from maize starch, has a molecular weight distribution such that 85% of the molecules have a molecular weight between 1638 and 45 000 dalton and 6% are less than 1638 and a number average molecular weight (Mn) of less than 6500 dalton. Glucose residues in icodextrin are joined largely through α-1,4 links, but there is a small degree of branching through α-1,6 links. Thus the structure of icodextrin is similar to that of glycogen, except the latter has a much higher degree of branching through α-1,6 links.

Carbohydrates with starchlike structures are substrates for α-amylase found in pancreatic juice, saliva, and plasma. Alpha-amylase readily hydrolyzes these carbohydrates to disaccharides, maltose (α-1,4 link), and isomaltose (α-1,6 link). The disaccharides are metabolized to glucose by specific enzymes, maltase and isomaltase, found in the small intestine, kidney, and a variety of other mammalian tissues (1). Thus it might be expected that icodextrin in the systemic circulation would be hydrolyzed by α-amylase, predominantly to maltose with some

Correspondence to: D.S. Davies, Department of Clinical Pharmacology, Royal Postgraduate Medical School, Ducane Road, London, W12 0NN, U.K.

isomaltase, which are then metabolized to glucose. If icodextrin enters cells, then it may serve as a substrate for the enzymes of glycogen metabolism, namely, glycogen phosphorylase and the debranching enzymes.

A starch-derived polymer of molecular weight 900 dalton was tested as an intraperitoneal osmotic agent in bilaterally nephrectomized dogs (2). It was effective but extensively absorbed into the systemic circulation. No significant metabolism of the polymer was found in peritoneal dialysate, but rapid hydrolysis was seen when it was added to dog serum. Serum polymer reached steady-state levels after 4 days of treatment, and it was shown that hydrolysis products of polymer, such as maltose, maltotriose, and maltotetrose, produced in the blood were cleared by dialysis into the peritoneal cavity. When treatment with polymer was discontinued, serum levels fell rapidly to normal.

A glucose polymer with the same chemical structure as icodextrin and a similar molecular weight profile (Caloreen) is widely used as an oral nutrient in the management of patients with renal (3) and hepatic failure (4). It is well tolerated, palatable, and readily hydrolyzed to glucose. The utility of glucose polymers for parenteral nutrition was investigated by a number of groups in animals and in man (5–7). These studies demonstrated the safety of the intravenous infusions, but also showed that a large portion of the dose (40% – 50%) was rapidly excreted unchanged in urine, severely limiting its value in parenteral nutrition (8). These studies demonstrated that carbohydrates with structures similar to icodextrin are cleared from the systemic circulation by the kidneys and metabolism to smaller fragments, eventually to glucose. In renal failure, systemic elimination would be by metabolism.

A glucose polymer prepared from starch was developed by Abbott Laboratories in the early 1980s. Its average molecular weight (Mw) was lower than icodextrin (7000 versus 20 000 dalton), and it was more readily absorbed from the peritoneal cavity. Analysis of plasma from treated patients confirmed that polymer absorbed into the systemic circulation was metabolized to maltose and maltotriose (9).

The fate of icodextrin administered in solution into the peritoneal cavity will depend on three situations: (1) the metabolic stability of the polymer in the peritoneal fluid; (2) the degree of absorption into the systemic circulation; (3) renal and metabolic elimination from the systemic circulation.

Movement of molecules from the peritoneal cavity into the blood stream can be by diffusion across the peritoneum or absorption through the lymphatic system. Studies with large molecules such as albumin have established that clearance from the peritoneum is some 40 times greater than from blood to peritoneum, and this has been attributed to lymphatic flow (10). The molecular weight cutoff for transmembrane transfer has not been accurately established and will probably vary with species and the condition of the peritoneum. However, the published data on absorption of molecules from the peritoneum indicate that the majority of molecules in icodextrin are too large for transfer across the peritoneum and will enter the blood stream via the lymphatic system (11). Slow absorption of icodextrin via the lymphatic system would be in keeping with its prolonged osmotic effect in continuous ambulatory peritoneal dialysis (CAPD) as shown by the almost constant osmolality of glucose polymer solutions in the peritoneal cavity over 12 hours (12). Icodextrin in the systemic circulation would be eliminated by metabolism and renal excretion as described above.

ANALYTICAL METHODS

An assay was developed to separate and analyze icodextrin and its metabolites in plasma, dialysis fluid, and urine samples (12). Briefly, icodextrin and components derived from its metabolism are separated according to molecular weight, by gel permeation chromatography. Carbohydrates in the column eluate are measured with an on-line specific detection system. Orcinol and sulphuric acid are mixed with the eluate, and the resulting chromophor is measured in a spectrophotometer. Concentrations of individual oligomers consisting of 1 – 10 glucose units (G1 – G10) and a high molecular weight species (>G10) are expressed in milligrams per milliliter and as a percent of the total carbohydrate in a sample.

KINETIC STUDIES OF GLUCOSE POLYMERS CONDUCTED DURING THE DEVELOPMENT OF ICODEXTRIN

A number of studies were conducted in patients during the development of icodextrin with glucose polymers identical in chemical structure to icodextrin but of different molecular weight profiles. Data obtained with these polymers are relevant to the kinetics and metabolism of icodextrin.

Stability of Glucose Polymer in Peritoneal Fluid: In studies briefly reported by Mistry (11), glucose polymer of Mw 7000, Mn 960 dalton was incubated with dialysate fluid obtained from 3 patients following overnight dialysis with glucose solutions. Over a period of 6 hours the percent of total carbohydrate in the high molecular weight fraction showed only very small decreases, and there were only minor increases in fractions G1 – G10 (Table 1). These results confirm the absence of significant α-amylase activity in dialysate fluid as found by Rubin and colleagues (2) in dogs.

Absorption of Glucose Polymer from the Peritoneal Cavity in Patients: A large number of studies were conducted on the absorption of carbohydrate in CAPD patients during the development of icodextrin (11). The absorption of a glucose polymer with a molecular weight profile similar to icodextrin (Mw 16 800, Mn 5000 dalton) was described by Mistry *et al.* (12). In 5 patients the mean percent of infused carbohydrate absorbed was 14.4% at 6 hours and 28.1% at 12 hours. In the same study, mean values for the absorption of glucose (1.36%) were 61.5% at 6 hours and 83.4% at 12 hours.

Metabolism of Glucose Polymer by Human Serum: Glucose polymers of differing molecular weight profiles were hydrolyzed to maltose (G2), maltotriose (G3), and G4 probably by α-amylase (11).

Plasma Levels of Glucose Polymer and Metabolites: Glucose polymer and metabolites arising from hydrolysis were monitored in plasma from CAPD patients treated with intraperitoneal solutions of polymers of various molecular weights (11,12). These studies show the appearance of high molecular weight material (including the original polymer molecules) as well as hydrolysis products, particularly maltose, maltotriose, and maltotetrose arising from the action of α-amylase as seen in the *in vitro* incubations with polymer (see above).

A study (11) in which a 7.5% solution of glucose polymer (Mw 22 000, Mn 7000 dalton) with added 0.35% glucose (final Mw 20 000, Mn 2900 dalton) was used for the overnight dwell for 10 days showed polymer and maltose and maltotriose reaching steady state at 4 – 8 days of treatment. When treatment with polymer solutions was stopped and peritoneal dialysis was continued with glucose solutions, high molecular weight material and maltose and maltotriose fell to near predose levels in 6 days. When the same treatment was used for 12 weeks, similar steady-state levels of total polymer-related material, maltose, and maltotriose were achieved and maintained for the entire treatment period.

The metabolites of glucose polymer are removed from the circulation by a combination of peritoneal dialysis and further metabolism. It appears that G1 – G4 readily cross the peritoneum into the dialysate but there is a sharp cutoff at G4 with little G5 and above being found (11). In the absence of uniformly labeled glucose polymer, it is not possible to measure the relative importance of metabolism and dialysis to the elimination of polymer metabolites from the systemic circulation in patients with renal failure. Mistry *et al.* (12) estimated the peritoneal clearance of maltose from plasma to be 3.5 mL/minute.

The presence of residual renal function in CAPD patients leads to lower steady-state levels of polymer and its metabolites and as would be expected because of excretion in urine. It is of interest to note that maltose and isomaltose are present in plasma from patients with chronic renal failure, not treated with icodextrin, are not found in samples from subjects with functioning kidneys (13).

KINETIC STUDIES OF ICODEXTRIN IN THE MIDAS STUDY

In the MIDAS study [a 6-month multicenter clinical trial of iso-osmolar icodextrin solutions in CAPD (14)] in which patients were treated with a single daily exchange of 2 L of 7.5% icodextrin, plasma samples were obtained during visit 2 (pretreatment with icodextrin), visit 6 (1 month after commencement of treatment), visit 9 (3 months), and visit 12 (6 months) and analyzed for icodextrin and metabolites. Plasma samples were also obtained from the control group, treated with glucose solutions, at visit 2 and visit 12 and analyzed as for the icodextrin group.

Special studies were conducted at two centers (Manchester and Sheffield) to measure carbohydrate absorption during treatment with icodextrin and glucose, and a minor study was carried out on the metabolism of icodextrin in plasma obtained from CAPD patients.

TABLE 1
Incubation[a] of Glucose Polymer with Dialysate from CAPD Patients

	Patient 1			Patient 2			Patient 3		
Fraction[b]	0 hr	3 hr	6 hr	0 hr	3 hr	6 hr	0 hr	3 hr	6 hr
G1	2.4	2.5	2.4	5.6	5.8	5.0	4.7	4.7	4.7
G2	4.9	4.3	4.1	3.0	3.1	3.0	3.1	3.4	3.4
G3–10	55.5	55.8	55.7	50.2	51.9	52.6	52.2	52.9	53.0
G>10	37.3	37.6	37.9	41.4	39.6	39.4	39.9	39.1	38.8

[a] Incubation of 0.5 mL of dialysate obtained following overnight exchange with glucose solution with 0.5 mL of 5% solution of glucose polymer of Mw 7000 and Mn 950 dalton.
[b] Expressed as percent of total carbohydrate in sample.

Plasma Levels of Icodextrin and Metabolites in the MIDAS Study: Plasma concentrations of carbohydrate molecules found on visits 2 and 12 for the control and visits 2, 6, 9, and 12 for the icodextrin group are presented in Table 2. The data show steady-state levels of polymer-derived material (CHO–G1) of approximately 4.6 mg/mL, G2 of 1.1 mg/mL, and G > 9 of 1.8 mg/mL, and these are maintained for the duration of the trial (Figure 1).

Absorption of Carbohydrate—MIDAS Special Studies: Manchester: During special study weeks when the dwell time for icodextrin and the comparator glucose solutions were controlled to 8 hours, dialysate from the icodextrin and glucose groups was analyzed for polymer and metabolites. Total carbohydrate lost from the dialysate was calculated and is presented in Table 3. Eleven patients treated with 7.5% icodextrin solutions for 8 hours lost a mean of 19.6% of the infused carbohydrate from the peritoneal cavity. This compares with a mean of 83.6% absorbed carbohydrate in 7 patients treated with strong glucose (6 on 3.86%, 1 on 2.27% glucose). In this study the mean carbohydrate absorbed per milliliter of ultrafiltrate was 102 mg for glucose and 49 mg for icodextrin.

Sheffield: The design was the same as the Manchester study except a dwell time of 12 hours was used. Mean data on the absorption of carbohydrate are presented in Table 3. The control group of 16 patients treated with 1.5% glucose solutions absorbed a mean of 83.1% of total carbohydrate in 12 hours. Absorption of carbohydrate in the icodextrin group of 20 patients was 33.5%.

These studies also showed that metabolites of icodextrin are removed from the systemic circulation by dialysis. Significantly more maltose (G2 or DP2) and intermediate molecular weight species (G3–G9) were found in the dialysate after icodextrin treatment than in the starting solution of icodextrin or in dialysate after treatment with glucose solutions.

Metabolism of Icodextrin in Human Serum: Icodextrin was added to samples of human plasma from CAPD patients treated with glucose solutions to give a final concentration of polymer of approximately 5 mg/mL. The samples were incubated at 37°C for up to 72 hours and analyzed for polymer and metabolites as described above. The results presented for a typical incubation in Table 4 show a rapid decline of high molecular weight molecules (G > 9) to 50% of the starting value in just over 2 hours and a rise in G2 and G3–9 as would be expected from the action of plasma α-amylase.

Steady-State Stop/Start Study: Plasma levels of icodextrin and maltose were measured in 12 patients who stopped once-a-day treatment with the polymer after approximately 2 years. Icodextrin-related material (4.8 mg/mL) and maltose (1.1 mg/mL) fell to pretreatment levels in 7 – 10 days (Figure 2). When treatment with icodextrin was recommenced after 22 days, plasma levels returned to the previous steady-state levels within 7 – 10 days.

CONCLUSIONS

Icodextrin in solution in the peritoneal cavity is absorbed into the blood stream, probably via the lymphatic system. The extent of absorption depends on the dwell time of the solution; about 20% of total carbohydrate is absorbed in 8 hours, and this rises to 34% at 12 hours. There is no evidence of metabolism of glucose polymers like icodextrin in the peritoneal cavity. Icodextrin in the systemic circulation is hydrolyzed, probably by plasma and tissue α-amylase, to oligosaccharides, such as maltose, isomaltose, maltotriose, and maltotetrose. These may be further metabolized, eliminated by peritoneal dialysis, or, if the patient has residual renal function, excreted in urine.

In CAPD patients treated with one exchange daily of 7.5% icodextrin and 3 – 4 exchanges of glucose

TABLE 2
Plasma Carbohydrate Levels in the MIDAS Study

	Mean ± SD Plasma Carbohydrate (mg/mL)					
	Glucose		Icodextrin			
Fraction	Predose (98)[a]	6 months (42)	Predose (91)	1 month (80)	3 months (72)	6 months (53)
G2	0.03±0.01	0.03±0.01	0.04±0.04	1.20±0.38	1.00±0.035	1.06±0.33
G3–9	0.02±0.01	0.03±0.01	0.02±0.04	1.84±0.61	1.67±0.50	1.76±0.56
>G9	0.27±0.09	0.30±0.07	0.29±0.10	1.83±0.64	1.73±0.63	1.84±0.61
CHO–G1[b]	0.32±0.10	0.36±0.08	0.35±0.15	4.87±1.55	4.40±1.37	4.65±1.39
Total CHO	1.20±0.58	1.27±0.40	1.18±0.33	5.95±1.55	5.40±1.40	5.59 ±1.41

[a] Number of patients.
[b] CHO is total carbohydrate.

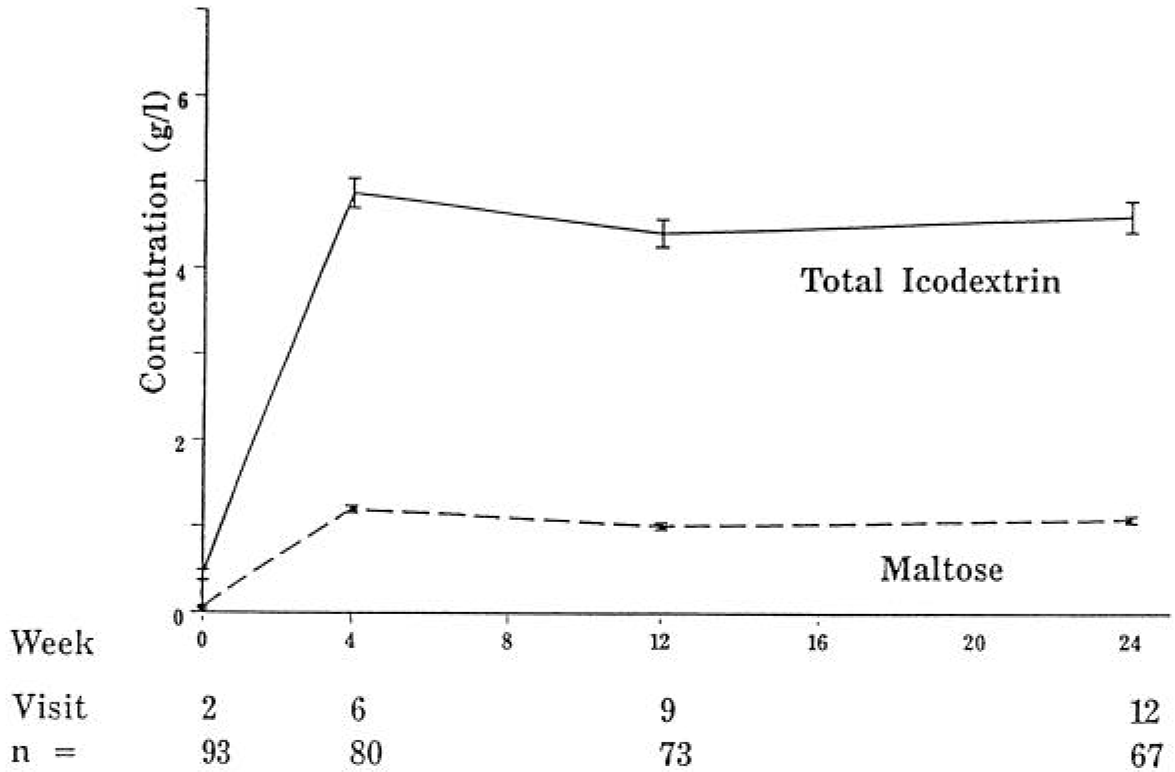

Figure 1 — Plasma levels of icodextrin and maltose in CAPD patients using solutions of the polymer once a day for 6 months.

TABLE 3
Total Carbohydrate Absorption from the Peritoneal Cavity of CAPD Patients

Center	Agent	Solution[a] (n)	Dwell Time	Volume Out (mean±SD)	Carbohydrate Lost g±SD	Carbohydrate Lost %±SD
Manchester	Glucose	3.63% (7)[b]	8 hours	2608±280	62.3±11.7	85.6±5.8
	Icodextrin	7.5% (11)	8 hours	2600±278	29.4±14.6	19.6±9.7
Sheffield	Glucose	1.5% (16)	12 hours	1853±384	24.9±2.7	83.1±9.0
	Icodextrin	7.5% (20)	12 hours	2569±360	50.2±14.2	33.5±9.5

[a] 2 L.
[b] Six patients on 3.86% and one on 2.27% solution.

TABLE 4
Incubation[a] of Icodextrin with Human Plasma

Fraction[b]	Control[c]	0	2	6	16	24	48	72
		Incubation Time (hours)						
G1	86.2	16.5	17.3	17.3	18.0	18.2	18.2	18.5
G2	2.2	0.8	5.4	10.9	20.9	23.5	25.1	25.9
G3–9	0.6	2.9	30.1	33.0	29.9	28.6	28.9	29.4
>G9	11.0	80.1	47.3	38.7	31.4	29.6	27.7	26.3
Carbohydrate (mg/mL)	0.9	5.8	5.7	5.7	5.6	5.0	5.4	5.4

[a] Icodextrin added to plasma from a CAPD patient to give a total carbohydrate concentration of approximately 5 mg/mL.
[b] Expressed as percent of total carbohydrate in sample.
[c] Plasma before addition of icodextrin.

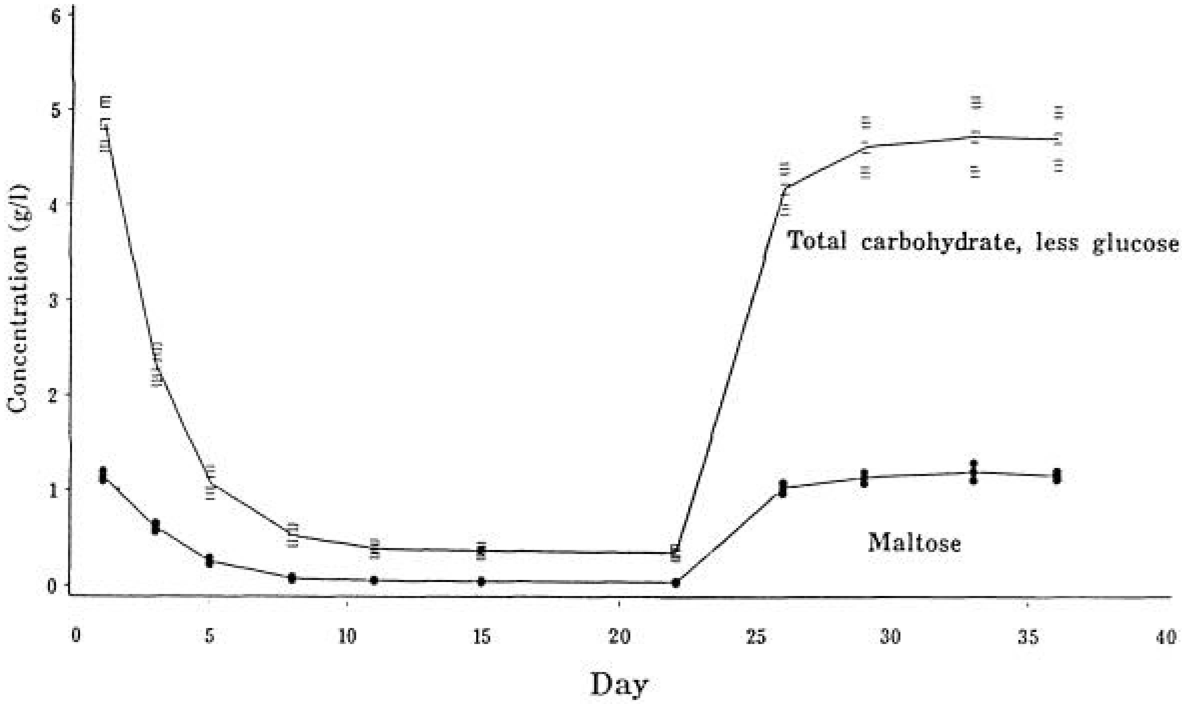

Figure 2 — Plasma levels of icodextrin and maltose in 12 patients who stopped using solutions of the polymer for CAPD after 2 years (time 0) and recommencing using it after 22 days.

solutions, steady-state levels of polymer and metabolites are established in 7 – 10 days and these have been shown to be maintained for periods up to 2 years. When treatment with icodextrin is stopped, and patients are maintained on glucose solutions, plasma levels of icodextrin and metabolites fall rapidly to normal in 7 – 10 days. These results strongly suggest that there is no capacity-limited deep compartment for the storage of icodextrin in the human body and provide important information supporting the safety in use of icodextrin in CAPD. In addition, unlike modified starches used as plasma expanders, no evidence was found for the tissue storage of icodextrin in the preclinical safety studies in rats and dogs.

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CHAPTER
TEN

REGULATION OF PLASMA OSMOLALITY

Syndromes of hypoosmolality and hyperosmolality can produce serious neurologic symptoms and death (see Chaps. 21 to 24). To prevent this, the plasma osmolality (P_{osm}) is maintained within narrow limits by appropriate variations in water intake and water excretion. In this chapter, we will describe the sources of water intake and sites of water loss from the body and the roles of ADH, thirst, and renal water excretion in the regulation of P_{osm}.

WATER BALANCE

In the steady state, water intake equals output (Table 10-1). A large fraction of the water output involves *obligatory losses* from the skin and respiratory tract and in the urine and stool. Approximately 900 ml/day is lost by the evaporation of water from the moist surfaces of the skin and respiratory tract. The heat required for the evaporation of these fluids, 0.58 kcal/1.0 ml of water, normally accounts for 20 to 25 percent of the heat lost from the body, the remainder occurring by radiation and convection [1]. These processes result in the elimination of the heat produced by body metabolism and prevent the development of hyperthermia.

In contrast to these "insensible" losses, sweat can be called a "sensible" loss. Sweat is hypotonic fluid (Na^+ concentration equals 30 to 50 meq/l)

Table 10-1 Typical daily water balance in a normal man, assuming a low rate of sweat production†

Water intake, ml/day		Water output, ml/day	
Source		Source	
Ingested water	1400	Urine	1500
Water content of food	850	Skin	500
Water of oxidation	350	Respiratory tract	400
		Stool	200
Total	2600		2600

†Under conditions of increased sweat production, the water losses from the skin can increase markedly, occasionally exceeding 5 l/day. When this occurs, thirst is stimulated, resulting in an appropriate increase in the volume of ingested water.

secreted by the sweat glands in the skin. It plays an important role in thermoregulation as the secretion and subsequent evaporation of sweat result in the loss of heat from the body. In the basal state, sweat production is low but it can increase markedly when endogenous heat production is enhanced, e.g., by exercise, fever, or hyperthyroidism, or in the presence of high external temperatures [1]. For example, a subject exercising in a hot, dry climate can lose as much as 1500 ml/h as sweat.

The obligatory renal loss is directly related to solute excretion. If, to remain in the steady state, a subject has to excrete 600 mosmol of solute per day (mostly Na^+,K^+, NH_4^+, Cl^-, and urea) and the maximum urine osmolality is 1200 mosmol/kg, the excretion of the 600 mosmol will require a minimum volume of 500 ml/day.

Only small amounts of water are lost in the stool, averaging 100 to 200 ml/day. However, this may by increased in patients with increased gastrointestinal losses due to vomiting or diarrhea.

To maintain water balance, water must be taken in to replace these losses (Table 10-1). Water intake is derived from three sources: (1) ingested water; (2) water contained in foods, e.g., meat is roughly 70 percent water and certain fruits and vegetables are almost 100 percent water; and (3) water produced from the oxidation of carbohydrates, proteins, and fats. If the latter two sources account for 1200 ml/day and the obligatory water loss is 1600 ml/day, then 400 ml must be ingested by drinking. Humans usually drink more than this minimum requirement, and the extra water is excreted in the urine.

REGULATION OF PLASMA OSMOLALITY

The normal plasma osmolality (P_{osm}) is 275 to 290 mosmol/kg and is determined by the relationship between body solute and body water (see page 27). The P_{osm} usually is held within narrow limits as variations of only 1 to 2 percent initiate mechanisms to return the P_{osm} to normal. These alterations in osmolality are sensed by receptor cells in the hypothalamus which induce appropriate changes in thirst and ADH secretion, i.e., in water intake and water excretion (see Chap. 8).

In terms of water balance, water retention, e.g., after a water load, decreases the P_{osm}, and a water deficit, e.g., due to hypotonic sweat loss after exercise on a hot day, increases the P_{osm}. These changes in water balance must be differentiated from conditions of isotonic fluid loss, e.g., diarrhea, in which solute and water are lost proportionately, producing no change in the P_{osm}.

The body responds to a water load by suppressing ADH secretion and thirst, resulting in the formation of a dilute urine and the excretion of the excess water (see Chap. 6 and below). The peak diuresis is delayed for 90 to 120 min, the time necessary for the metabolism of previously circulating ADH. As will be seen, the kidney can excrete up to 15 to 20 liters of water per day. Therefore, *persistent water retention resulting in hypoosmolality occurs, with rare exceptions, only in patients with reduced renal water excretion* (see Chap. 22).

The correction of a water deficit (hyperosmolality) requires the intake and retention of exogenous water. This is achieved by increases in thirst and ADH secretion which are induced by the elevation in the P_{osm}. In contrast to the response to hypoosmolality, in which renal water excretion is of primary importance, increased thirst is the major defense against hyperosmolality. Although the kidney can minimize water excretion by the production of a concentrated urine, a water deficit can be corrected only by increased dietary intake. An example of the efficiency of the thirst mechanism occurs in patients with complete central diabetes insipidus who, because they secrete no ADH, may excrete more than 15 liters of water per day. Despite this, the P_{osm} remains near normal because the thirst mechanism augments water intake to match output. Thus, *symptomatic hyperosmolality will not occur in a patient with a normal thirst mechanism and access to water* (see Chap. 23).

When the P_{osm} is increased by an increase in body solute, e.g., after a Na^+ load, both the volume and osmoregulatory systems come into play. The increment in Na^+ stores expands the effective circulating volume, promoting the renal excretion of the excess Na^+. Thirst also is stimulated, and the increase in water intake both lowers the P_{osm} toward normal and further expands the volume, thereby enhancing the stimulus to renal Na^+ excretion.

RENAL WATER EXCRETION AND REABSORPTION

In the kidney, the bulk of the filtered water is reabsorbed passively down an osmotic gradient created by NaCl transport. This serves to maintain the volume of the extracellular fluid. In addition, the kidney contributes to the stability of the P_{osm} by excreting or reabsorbing water without solute. This function is primarily mediated by the presence (water conservation, high U_{osm}) or absence

Table 10-2 Relation of urine osmolality and Na^+ concentration to plasma osmolality and the effective circulating volume

	Urine†		
	$[Na^+]$	Osmolality	ADH release
Plasma osmolality			
Increased	0 – ↑††	↑	↑
Decreased	0 – ↓	↓	↓
Effective circulating volume			
Increased	↑	↓	↓
Decreased	↓	↑	↑

†The urine osmolality is determined primarily by the availability of ADH. Since ADH release is controlled by osmolality and volume, the urine osmolality is affected by both of these parameters. Urinary Na^+ excretion, on the other hand, is mostly a function of the effective circulating volume, with a lesser contribution from the plasma osmolality or the plasma Na^+ concentration.

†† ↑ = increase
↓ = decrease
0 = no change

(water excretion, low U_{osm}) of ADH. Since ADH secretion is controlled by the P_{osm} and the effective circulating volume (see Chap. 8), the U_{osm} is affected by both of these parameters (Table 10-2). For example, a water load lowers the P_{osm} which suppresses ADH release, resulting in the formation of a dilute urine and the excretion of the water load. In contrast, ADH has no direct effect on Na^+ reabsorption, urinary Na^+ excretion being determined primarily by the effective circulating volume and, to a lesser degree, the plasma Na^+ concentration (see Chap. 9).

Measurement of Renal Water Excretion

The quantitative importance of ADH on water excretion is depicted in Table 10-3. To maintain solute homeostasis, solute excretion must equal the daily solute load (primarily Na^+ and K^+ salts and urea). In a subject excreting 700 mosmol of solute per day, the urine volume can vary 20-fold, depending upon the availability of ADH. For example, in the absence of ADH, the minimum U_{osm} may be 70 mosmol/kg, resulting in the excretion of the 700 mosmol of solute in 10 liters of water. In a normal subject, this degree of polyuria is rarely seen and occurs only after a massive water load. More commonly, there is a moderate amount of ADH present, and the U_{osm} is somewhere between the extremes of 70 mosmol/kg (no ADH) and 1400 mosmol/kg (maximum ADH). If this subject had to excrete 2000 ml of water to remain in water balance, the average U_{osm} would be 350 mosmol/kg, that is 700 mosmol of solute in 2000 ml. This would require a submaximal ADH effect.

Table 10-3 Effect of ADH on urine volume in a subject excreting 700 mosmol of solute per day

Solute excretion = 700 mosmol/day

ADH	U_{osm}, mosmol/kg	Urine volume, l/day
0	70	10
++	350	2
+++	1400	0.5

In addition to ADH, which determines the urine osmolality, water excretion also is affected by solute excretion (Fig. 10-1). In the absence of ADH, the daily urine volume is 10 liters if 700 mosmol of solute is excreted but only 5 liters if 350 mosmol of solute is excreted, that is, 350 mosmol of solute at 70 mosmol/kg.

Since water excretion can vary widely without change in the U_{osm}, it is clear that the U_{osm}, which in a hypotonic urine reflects the kidney's ability to dilute the urine, is not an accurate estimate of its quantitative ability to excrete water. To measure the amount of solute-free water that the kidney can excrete per unit time, one can calculate the *free-water clearance* (C_{H_2O}). If the urine is hypotonic to plasma, the urine volume (V, in ml/min or l/day) can be viewed as having two components, one that contains the urinary solute in a solution that is isotonic to plasma (the osmolal clearance, C_{osm}) and one that contains the solute-free water (the free-water clearance, C_{H_2O}). The isotonic fraction is equal to the osmolal clearance because, from the formula for clearance (see page 59), $C_{osm} = (U_{osm} \times V)/P_{osm}$, if the U_{osm} is the same as the P_{osm}, then the C_{osm} will equal the urine volume. Therefore,

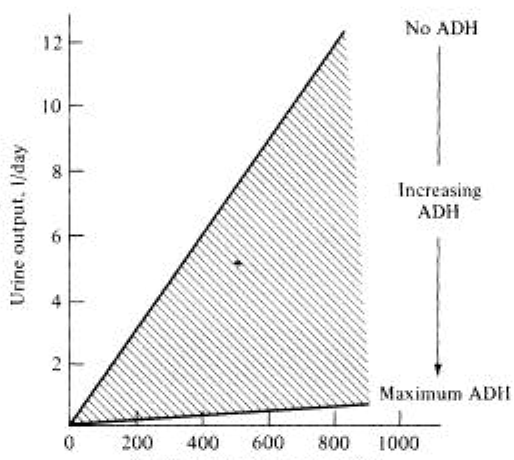

Figure 10-1 Effects of ADH and solute excretion on water excretion. It is assumed that the U_{osm} is 70 mosmol/kg in the absence of ADH and 1400 mosmol/kg with maximum ADH effect.

$$V = C_{osm} + C_{H_2O}$$

or

$$C_{H_2O} = V - C_{osm}$$

For example, if, from Table 10-3,

$$P_{osm} = 280 \text{ mosmol/kg}$$
$$U_{osm} = 70 \text{ mosmol/kg}$$
$$V = 10 \text{ l/day}$$

then

$$C_{H_2O} = 10 - (70 \times 10/280)$$
$$= 7.5 \text{ l/day}$$

Thus, of the 10 liters of urine being excreted, 7.5 liters exists as free water and 2.5 liters as an isotonic solution.

In the clinical setting, the excretion of large volumes of dilute urine may be *appropriate*, e.g., due to a water load, or *inappropriate*, due to the absence of ADH or renal resistance to its effects. In either case, the loss of solute-free water tends to raise the P_{osm} unless accompanied by an increase in water intake.

Physiologic factors affecting C_{H_2O} The excretion of water by the kidney occurs in two basic steps (see Chap. 6):

1. Solute-free water is generated by NaCl reabsorption without water in the medullary and cortical aspects of the ascending limb of the loop of Henle.
2. This water is then excreted by keeping the collecting ducts impermeable to water.

In normal subjects, the generation of free water is primarily dependent upon the volume of water presented to the ascending limb (see below). Collecting duct impermeability to water requires the absence of ADH and probably the presence of cortisol.

Relation between effective circulating volume depletion and C_{H_2O} Depletion of the effective circulating volume, due to true volume depletion, e.g., vomiting, to the extravascular sequestration of fluid, e.g., cirrhosis of the liver with ascites, or to a primary decrease in cardiac output, e.g., heart failure (see Chap. 9), can impair C_{H_2O} in two ways [2]. First, hypovolemia is a potent stimulus to ADH secretion, resulting in enhanced water permeability of the collecting ducts. Second, in response to volume depletion, there may be a decrease in GFR and an increase in fractional proximal Na^+ and water reabsorption as the kidney tries to correct the volume deficit by conserving Na^+ and water [2] (Table 10-4). As a result of this and of continued water reabsorption in the descending limb of Henle, the delivery of water to the diluting segment (the ascending limb of

Table 10-4 Hypothetical example of the delivery of water to the different nephron segments in normal and hypovolemic states

	Normal†	Hypovolemia
GFR	100	70
Fractional proximal water reabsorption	70%	85%
Loop of Henle water delivery	30	10.5
Loop and distal tubular water reabsorption	13	7.0
Collecting duct water delivery	17	3.5

†The normal values are taken from Table 9-2. All units are milliliters per minute except for fractional proximal reabsorption.

Henle) is markedly reduced. Since solute-free water generation is limited by the volume of water presented to the ascending limb, it too will fall during volume depletion. An effect similar to hypovolemia may be seen in patients with renal failure in whom delivery to the ascending limb is diminished because of the decrease in GFR.

In addition to reducing C_{H_2O}, the reduction in distal delivery can impair the ability to excrete a hypotonic urine, even in the absence of ADH. Consider the experiment diagramed in Fig. 10-2. A dog was given a water load so that the

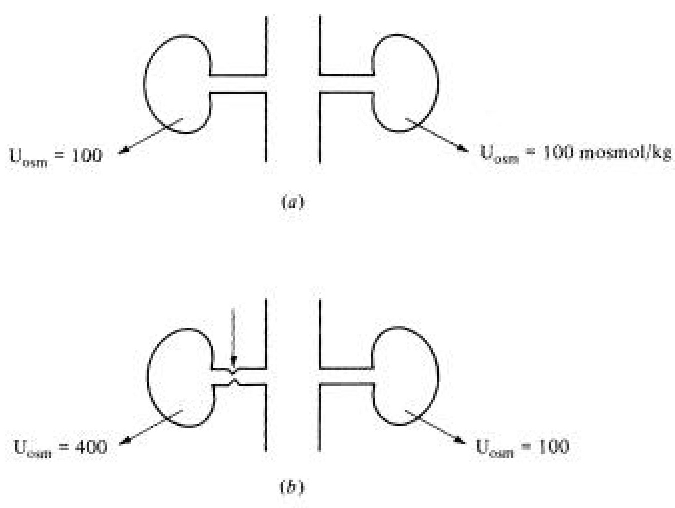

Figure 10-2 Excretion of a concentrated urine in the absence of ADH in the dog. (*a*) After a water load, the urine osmolality falls to 100 mosmol/kg as ADH secretion is inhibited. (*b*) If one renal artery is constricted to reduce the GFR to 50 to 70 percent of normal, the osmolality of the urine from the constricted kidney can reach 400 mosmol/kg. The urine from the control kidney remains dilute, suggesting the continued absence of ADH.

U_{osm} was less than 100 mosmol/kg and, presumably, endogenous ADH secretion was inhibited. When one renal artery was constricted to reduce the GFR by 25 to 50 percent, the osmolality of the urine from that kidney rose to as high as 400 mosmol/kg [3]. Thus, in the absence of ADH (the U_{osm} from the control kidney remained less than 100 mosmol/kg), a mildly concentrated urine can be formed.

The ability to concentrate the urine in this situation probably is related to the fact that the collecting ducts are relatively, not totally, impermeable to water in the absence of ADH. If the osmolality of the urine entering the collecting ducts is 100 mosmol/kg, due to the reabsorption of NaCl without water in the ascending limb of Henle, then 75 percent of the water presented to the collecting ducts must be reabsorbed to raise the U_{osm} to 400 mosmol/kg. In normal subjects, collecting duct delivery may be 17 ml/min (Table 10-4). Thus, to increase the U_{osm} to 400 mosmol/kg, roughly 12.8 ml of water (75 percent of 17 ml) must be reabsorbed per minute, and this requires ADH. However, collecting duct delivery may be reduced to 3.5 ml/min in volume depletion (Table 10-4). In this setting, only 2.6 ml of water must be reabsorbed per minute; apparently this can be done without ADH.

Although some water can be reabsorbed in the collecting ducts without ADH, maximum urinary concentration, by full osmotic equilibration between the tubular fluid and the medullary interstitium, cannot be attained in the absence of ADH. As a result, the administration of ADH will further increase the U_{osm} owing to enhanced collecting duct water reabsorption.

These effects of volume on urinary dilution can have important clinical implications:

Case history 10-1 A 45-year-old male chronic alcoholic was brought into the emergency room in a comatose condition. No history was obtainable. On physical examination, the blood pressure was found to be 80/60 recumbent, 60/30 sitting. The skin turgor was poor. The laboratory data were:

$$\text{Plasma } [Na^+] = 165 \text{ meq/l}$$

$$U_{osm} = 420 \text{ mosmol/kg}$$

$$\text{Urine } [Na^+] = 2 \text{ meq/l}$$

$$\text{Urine output} = 60 \text{ ml/h}$$

On the basis of the physical findings and the low urinary Na^+ concentration, it was felt that the patient was volume-depleted. After volume repletion with half-isotonic saline, the urine osmolality fell to 107 mosmol/kg, with the urine output exceeding 400 ml/h. This polyuric response occurred despite the persistence of an elevated plasma Na^+ concentration. The administration of 5 units of aqueous vasopressin subcutaneously at this time increased the urine osmolality to 700 mosmol/kg and lowered the output to 60 ml/h. This response confirmed the diagnosis of central diabetes insipidus (absence of ADH due to failure of pituitary secretion) (see Chap. 23).

As seen in this patient, complete lack of ADH is characterized by the excretion of large volumes of dilute urine. When volume depletion is present, as when this patient was admitted to the hospital, the decrease in collecting duct delivery masked the severity of the disorder by increasing the urine osmolality (to 420 mosmol/kg) and reducing the urine output (to 60 ml/h). Since polyuria is the primary complaint of patients with diabetes insipidus, the latter effect of hypovolemia provides the rationale for the use of diuretics in this disease (see page 426).

Summary In humans, the maximum C_{H_2O} is 10 to 15 ml/min, or 15 to 20 l/day. Since the capacity for water excretion is so great, water retention, resulting in hypoosmolality and hyponatremia, rarely occurs unless the C_{H_2O} is reduced. From the above discussion, this can be due to reduced delivery to the diluting segments, e.g., due to volume depletion or renal failure, and/or to increased collecting duct water permeability, e.g., due to adrenal insufficiency or to the presence of ADH, as in the syndrome of inappropriate ADH secretion. Thus, these disorders, plus diuretics which directly inhibit NaCl reabsorption in the ascending limb, compose most of the differential diagnosis of hyponatremia (see Chap. 22).

Measurement of Renal Water Reabsorption

In addition to the formation of a hypotonic urine, the kidney is also able to excrete urine with an osmolality exceeding that of the plasma. If the urine is hypertonic, the urine volume (V) can be viewed as having two components: one containing all the urinary solute in an isotonic solution (the C_{osm}) and one containing the amount of free water that must have been removed from the urine by tubular reabsorption (the free-water reabsorption, $T^c_{H_2O}$) to raise the U_{osm} to the observed hypertonic value. In this setting,

$$V = C_{osm} - T^c_{H_2O}$$

$$T^c_{H_2O} = C_{osm} - V$$

In contrast to the C_{H_2O} which is equal to the volume of free water *excreted* per unit time, the $T^c_{H_2O}$ is equal to the volume of free water *reabsorbed* per unit time. For example, if a subject who has developed hyperosmolality due to a water deficit has the following values,

$$P_{osm} = 295 \text{ mosmol/kg}$$

$$U_{osm} = 885 \text{ mosmol/kg}$$

$$V = 1 \text{ ml/min}$$

then

$$T^c_{H_2O} = \left(885 \times \frac{1}{295}\right) - 1$$

$$T^c_{H_2O} = 2 \text{ ml/min}\dagger$$

Thus, 2 ml/min of free water is being added to the plasma. This tends to lower the P_{osm} back toward normal, an appropriate response to a water deficit.

Physiologic factors affecting $T^c_{H_2O}$ Renal water conservation is dependent upon the following (see Chap. 6):

1. The formation and maintenance of the medullary osmotic gradient
2. Equilibration of the urine with the hypertonic medullary interstitium

Medullary hypertonicity is produced by NaCl reabsorption without water in the ascending limb of Henle (ADH-independent) and by the medullary accumulation of urea (ADH-dependent). ADH also increases the water permeability of the collecting ducts, permitting osmotic equilibration with the interstitium.

$T^c_{H_2O}$ can be impaired by a defect in ADH release, decreased responsiveness of the collecting duct epithelium to ADH, or a primary abnormality in countercurrent function, preventing the maintenance of hypertonic interstitium. When one of these disturbances is present, water excretion increases and the patient may complain of polyuria. If these water losses are not replaced, hyperosmolality will ensue (see Chap. 23).

In humans, the maximum $T^c_{H_2O}$ is 1 to 2 ml/min. Although this is much less than the maximum C_{H_2O} of 10 to 15 ml/min, it must be emphasized that *the volume of water retained during the correction of a water deficit is dependent upon water intake, mediated by thirst, as well as on renal water conservation.* For example, suppose a normal subject develops a 1000-ml water deficit due to sweat loss after exercise on a hot day. The increase in the P_{osm} induced by the water loss stimulates both ADH release and thirst. If this subject excretes 600 mosmol of solute per day and the urine can be concentrated to 1200 mosmol/kg, the urine volume will be 500 ml. If water intake also is 500 ml, there will be no water retention and no replacement of the water deficit even though the kidney is conserving water maximally. To restore water balance, water intake must exceed output (urine plus insensible) by 1000 ml; this is achieved by the stimulation of thirst.

†These values also can be used to calculate the C_{H_2O}:

$$C_{H_2O} = V - C_{osm}$$

$$= 1 - \frac{885 \times 1}{295} = -2 \text{ ml/min}$$

Thus, -2 ml/min of free water is being excreted, another way of stating that 2 ml/min is being reabsorbed. This illustrates the inverse relationship between the C_{H_2O}, which measures water excretion, and the $T^c_{H_2O}$, which represents water reabsorption:

$$C_{H_2O} = -T^c_{H_2O}$$

Summary

The ability to excrete urine with an osmolality different from that of the plasma plays an important role in the maintenance of water balance and P_{osm}. If the P_{osm} is decreased, e.g., after a water load, ADH secretion is inhibited. This results in the excretion of a dilute urine which increases the P_{osm} to normal. If the P_{osm} is elevated, e.g., because of sweat loss, both ADH release and thirst are stimulated. The combination of renal water conservation (by excreting a concentrated urine) and an increase in water intake results in water retention and a decrease in P_{osm} to normal. The C_{H_2O} and $T^c_{H_2O}$ are quantitative measures of the ability of the kidney to excrete or conserve water, respectively.

PROBLEMS

10-1 Diarrheal fluid usually is isotonic to plasma even though its isotonic composition differs from that of the plasma. What effect will the loss of 2 liters of diarrheal fluid have on (*a*) the effective circulating volume; (*b*) urinary Na^+ excretion; (*c*) the plasma osmolality; (*d*) the plasma Na^+ concentration; (*e*) ADH secretion; (*f*) the urine osmolality; and (*g*) thirst?

If such a patient ingested water, what would happen to the plasma osmolality?

10-2 What is the relation between the plasma Na^+ concentration and urinary Na^+ excretion?

10-3 A patient with volume depletion due to vomiting has hyponatremia and hypoosmolality. What are the factors that may contribute to the inability to restore normal osmolality by excreting the excess water in the urine? What mechanisms would be responsible for an impaired ability to excrete water in a patient with hepatic cirrhosis and ascites?

10-4 The following data were obtained for a normal subject who had taken no fluids for 12 h. At the end of each 30-min collection period, the bladder was emptied and a blood specimen drawn.

Period	P_{osm}, mosmol/kg	Volume, ml/min	U_{osm}, mosmol/kg
1	286	0.5	1040

Calculate the free-water reabsorption ($T^c_{H_2O}$). After this control collection, the subject drinks 1200 ml of water, and six additional 30-min collections are made.

2	286	0.8	650
3	284	5.6	92
4	282	10.4	50
5	281	10.0	51
6	282	4.0	128
7	284	1.3	398

Calculate the free-water clearance (C_{H_2O}) from the collection in period 4. Explain the sequence of events that led to the changes in the U_{osm} and urine volume.

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CHAPTER

TWENTY-FOUR

HYPEROSMOLAL STATES – HYPERGLYCEMIA

PATHOPHYSIOLOGY

Hyperglycemia is a common clinical problem. In addition to producing a hyperosmolal state similar to hypernatremia, hyperglycemia may be associated with severe metabolic acidosis (ketoacidosis) and volume depletion, both of which can jeopardize the life of the patient. Although a complete discussion of the regulation of carbohydrate and fat metabolism is beyond the scope of this chapter (see Ref. 1), a review of the role of insulin and other hormones is essential to understanding the pathophysiology of these disorders.

Hyperglycemia

The glucose concentration in the extracellular fluid (ECF) is determined by the balance between production and utilization. Glucose production is dependent upon dietary intake, hepatic gluconeogenesis (using lactate, amino acids, and glycerol as substrates), and glycogenolysis (Fig. 24-1) [1,2]. This glucose can then be utilized for energy or stored, for future use, as glycogen in the liver and skeletal muscle.

In the normal subject, the extracellular supply of glucose is carefully regulated, as the plasma glucose concentration is maintained within narrow limits (60 to 100 mg/dl, fasting). Insulin, whose secretion from the pancreas varies directly with the plasma glucose concentration, plays a central role in this process as it affects both glucose production and utilization (Fig. 24-1).

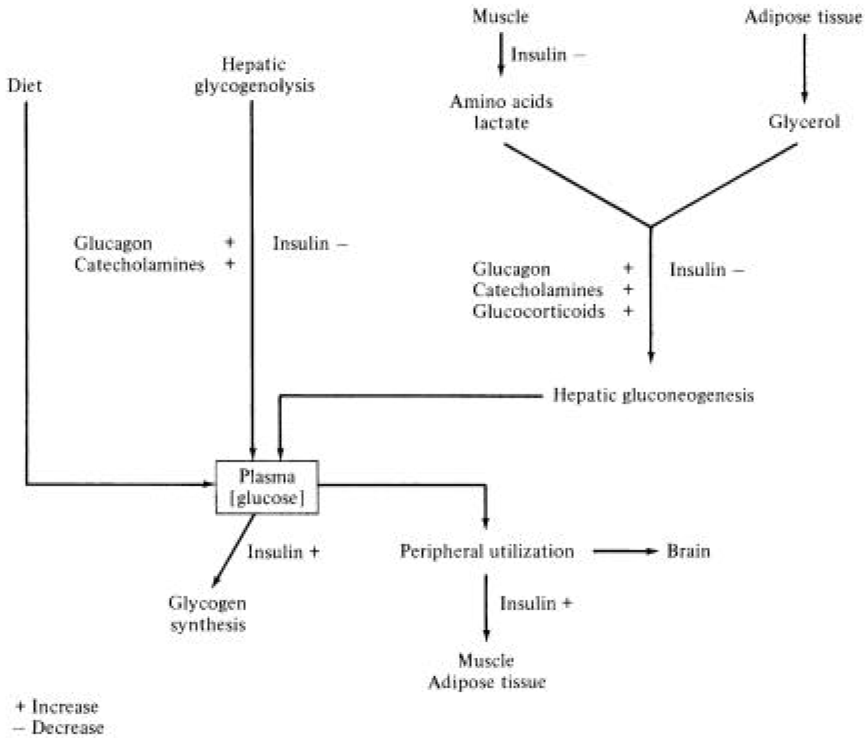

Figure 24-1 Hormonal regulation of carbohydrate metabolism. The factors governing glycerol release from adipose tissue are shown in Fig. 24-2.

Insulin acts to lower the plasma glucose concentration by reducing gluconeogenesis and glycogenolysis, i.e., production, and by enhancing glucose uptake by the liver, skeletal muscle, and adipose tissue, i.e., utilization. Insulin does not seem to be required for glucose uptake by the brain [3]. For example, the plasma glucose concentration rises after a carbohydrate meal, resulting in increased insulin secretion which returns the plasma glucose concentration to normal. On the average, 85 percent of the ingested glucose is taken up by the liver and stored as glycogen, with only 15 percent being delivered to the extrahepatic tissues [4]. The predominance of this hepatic effect may be related to the fact that insulin is released from the pancreas into the portal vein. Consequently, after a glucose meal the portal vein insulin concentration may be 3 to 10 times that in the peripheral circulation [5].

In contrast, insulin-deficient states are characterized by enhanced gluconeogenesis and glycogenolysis and by decreased glucose utilization. This is an appropriate response in fasting subjects since it serves to maintain an adequate supply of glucose for cerebral metabolism. However, when there is a nonphysiologic decrease in insulin secretion or when insulin resistance is present, e.g., due to obesity [6] or to insulin antibodies in a patient taking beef

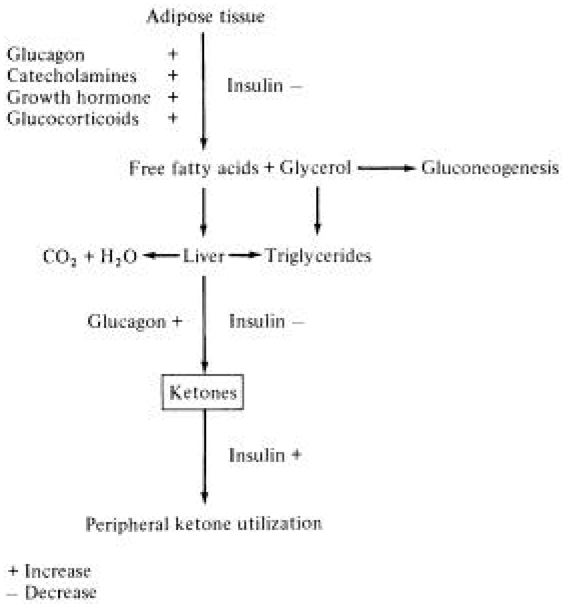

Figure 24-2 Hormonal control of ketone metabolism.

or pork insulin, hyperglycemia can ensue. This decrease in insulin availability usually is secondary to underlying diabetes mellitus but may be due to diffuse pancreatic disease, e.g., chronic pancreatitis, or to total pancreatectomy for carcinoma of the pancreas.

Ketoacidosis

Free fatty acids (FFA) are released from adipose tissue and then metabolized in the liver into triglycerides, $CO_2 + H_2O$, or ketones (acetoacetic acid, β-hydroxybutyric acid, and acetone) (Fig. 24-2). The latter two processes occur in the mitochondria of the hepatocyte whereas triglyceride synthesis takes place in the cytoplasm [7,8]. Hepatic ketone synthesis appears to be dependent upon two factors: (1) the rate of lipolysis which regulates the supply of free fatty acids and (2) the preferential conversion of FFA into ketones rather than triglycerides. This appears to be dependent upon the activity of the enzyme acylcarnitine transferase (ACTase) which facilitates the entry of free fatty acids into the mitochondria (Fig. 24-3).

As depicted in Fig. 24-2, ketogenesis is under extensive hormonal control, with insulin playing a major role [2,7,10]. Insulin is a potent inhibitor of ketone production, reducing both lipolysis and ACTase activity. Conversely, when insulin is absent, e.g., in fasting or uncontrolled diabetes mellitus, lipolysis and ACTase activity are enhanced (Fig. 24-3), resulting in ketoacid accumulation in the ECF and metabolic acidosis. (Acetone also can achieve high concentrations in the ECF but it is chemically neutral and does not contribute to the

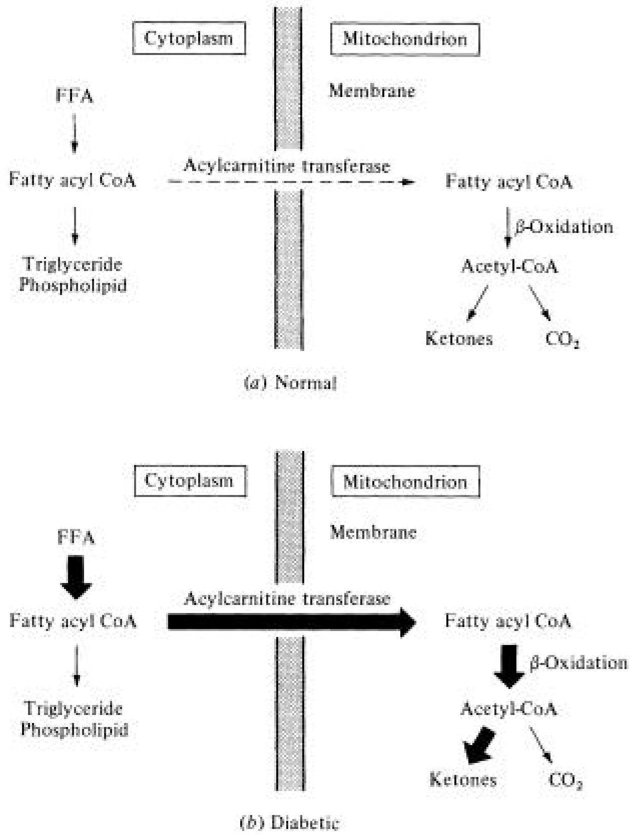

Figure 24-3 Possible model for the regulation of ketogenesis in diabetic acidosis. The pathways shown are highly simplified and schematized. In the normal state (*a*) free-fatty-acid delivery to the liver is low and fatty acid oxidation is inhibited at the level of the acylcarnitine transferase reaction. Fatty acids are therefore utilized primarily for triglyceride synthesis. In contrast, in diabetes mellitus (*b*), free-fatty-acid delivery is increased and the fatty acids are oxidized to ketone bodies through activation of the acylcarnitine transferase step. *(From J. D. McGarry and D. W. Foster, J. Clin. Invest., 52:877, 1973.)*

acidosis.) The importance of the increase in ACTase activity has been demonstrated by the ability of an ACTase inhibitor, (+)-decanoylcarnitine, to reverse experimental ketoacidosis without the administration of insulin [7]. In this setting, the plasma FFA concentration remains elevated but the FFA are not converted into ketones in the liver.

It should be noted that increased ketone production is not necessarily maladaptive. In the normal subject, skeletal muscle, the heart, and the kidney primarily utilize ketones and FFA for energy whereas the brain uses only glucose at the rate of approximately 150 g/day [9]. In the chronically fasting subject in whom the supply of glucose is reduced, the brain can switch over from glucose to ketones as its metabolic fuel [9]. This acts to conserve body protein stores since enhanced gluconeogenesis, much of which occurs from amino acids derived from protein breakdown, is not required to provide glucose to meet the energy needs of the brain. However, when there is a nonphysiologic decrease in insulin secretion, as in uncontrolled diabetes mellitus, ketone production far exceeds utilization, resulting in ketonemia and metabolic acidosis.

In summary, insulin deficiency (or resistance) is required for the development of hyperglycemia and ketoacidosis. In addition, other hormones, such as glucagon, catecholamines, glucocorticoids, and growth hormone, can affect carbohydrate and fat metabolism (Figs. 24-1 and 24-2) [1,2,10]. These hormones tend to counteract the effects of insulin by stimulating gluconeogenesis, glycogenolysis, and lipolysis, thereby increasing the extracellular supply of glucose and FFA. Glucagon also may directly promote ketone synthesis by enhancing ACTase activity [10]. Studies have suggested that, *in conjunction with insulin deficiency*, the endogenous hypersecretion of glucagon and catecholamines can contribute to the development of hyperglycemia and ketoacidosis in uncontrolled diabetes mellitus [10,11].

Volume Depletion

Glucosuria usually accompanies hyperglycemia. As the filtered load of glucose (GFR times plasma glucose concentration) exceeds tubular reabsorptive capacity, glucose remains in the tubular lumen and acts as an osmotic diuretic, resulting in the renal loss of electrolytes and water. In patients with severe hyperglycemia, the fluid loss may average 8 to 10 liters (almost 25 percent of the total body water) [12] and produce severe circulatory insufficiency.

Hyperglycemia and Plasma Na^+ Concentration

Since glucose penetrates cells slowly, an increase in the plasma glucose concentration raises the effective P_{osm} and causes water to move from the cells into the ECF. By dilution, this lowers the plasma Na^+ concentration. In theory, every 62 mg/dl increment in the plasma glucose concentration should draw enough water out of the cells to reduce the plasma Na^+ concentration 1 meq/l [13]. For example, if the plasma glucose concentration is 720 mg/dl (620 mg/dl greater than normal), the plasma Na^+ concentration should fall 10 meq/l from 140 to 130 meq/l. It is important to be aware of this situation because therapy must be directed toward hyperosmolality and not, as suggested by the presence of hyponatremia, toward hypoosmolality.

In certain clinical states, the plasma Na^+ concentration may differ from the value predicted from the increase in the plasma glucose concentration. Patients with diabetic ketoacidosis may have an exaggerated fall in the plasma Na^+ concentration due to hyperlipemia (see page 394). In other patients, the plasma Na^+ concentration may be normal or even elevated because of the preferential loss of water in excess of solute induced by the glucose osmotic diuresis (see page 100).

ETIOLOGY

There are two symptomatic, hyperglycemic syndromes in humans: *diabetic ketoacidosis* (DKA) and *hyperglycemic, nonketotic coma* (NKC). The absence of ketoacidosis in NKC appears to be due to the differential sensitivity of fat and glucose metabolism to the effects of insulin. Studies on the human forearm indicate that the concentration of insulin necessary to suppress lipolysis is only one-tenth that required to promote glucose utilization [14]. Consequently, with moderate insulin deficiency, there might be enough insulin available to block lipolysis but not enough to enhance glucose utilization. The result would be hyperglycemia without ketoacidosis. With more severe insulin deficiency, lipolysis would be increased and ketoacidosis would accompany the increase in the plasma glucose concentration. Consistent with this model are the findings of some observers of a higher plasma FFA concentration and a lower plasma insulin concentration in patients with DKA than in those with NKC [12,15,16]. In addition, DKA tends to occur in patients who produce little or no endogenous insulin, e.g., in juvenile diabetes mellitus, whereas NKC occurs most commonly in patients in whom insulin levels are reduced, but not absent, and who have either no history or one of mild, maturity-onset diabetes mellitus [12,17,18].

It should be noted, however, that other observers have been unable to demonstrate these differences in the plasma concentrations of insulin and FFA and have suggested that differences in portal vein insulin levels are more important [18–20]. In this hypothesis, there is enough insulin present to suppress hepatic ketone synthesis in NKC but not in DKA.

Most frequently, the onset of DKA is due to omission of insulin therapy or failure to augment insulin dosage when the plasma glucose concentration is poorly controlled. DKA also can be precipitated by various stresses, e.g., infection, surgery, or emotional trauma, and this may be the initial mode of presentation in previously undiagnosed patients, particularly juvenile diabetics.

In contrast to DKA, NKC usually occurs in older patients (average age 60 to 65) who are not insulin-dependent. It can be precipitated by infection, renal failure, glucocorticoid therapy, or acute glucose loading [12,21–23]. The latter situation can occur after intravenous hyperalimentation [21] or peritoneal dialysis with 7% glucose solutions (dialysate osmolality of 665 mosmol/kg) [23]. This complication of peritoneal dialysis has become less frequent since the 7% solution is no longer available for use. Since NKC may occasionally be seen with the less hypertonic solutions, e.g., with 4.25% glucose, the plasma glucose concentration should be carefully monitored in any patient on peritoneal dialysis.

Both DKA and NKC can be induced in patients who do not have diabetes mellitus. This may occur after acute glucose loading [22] or after the administration of drugs which inhibit insulin release, e.g., diazoxide (Hyperstat) [16,24], diphenylhydantoin (Dilantin) [25], and thiazide diuretics [26], or which antagonize insulin action, e.g., glucocorticoids [27].

Mannitol

Mannitol is a nonreabsorbable sugar which can be given as a hypertonic solution to augment urine output in oliguric patients. Because it acts as an osmotic diuretic, mannitol can produce hypernatremia if the renal water loss is not replaced. However, in patients with renal failure, the mannitol may not be excreted in the urine. To the extent that it is retained in the extracellular fluid, mannitol will increase the P_{osm} and lower the plasma Na^+ concentration in a manner similar to hyperglycemia.

SYMPTOMS

Hyperglycemia is associated with hyperosmolality, volume depletion, and, in DKA, metabolic acidosis, and the patient may suffer from symptoms due to each of these abnormalities. The severity of these symptoms is proportional to both the degree and the duration of the hyperglycemia.

In alert patients, polyuria, polydipsia, and weight loss are the most prominent complaints, and this triad should alert the physician to the possibility of hyperglycemia. These symptoms are due to the glucose osmotic diuresis and to the increase in the P_{osm}.

The neurologic abnormalities induced by hyperosmolality are similar to those seen with hypernatremia and include lethargy, twitching, obtundation, seizures, and coma (see Chap. 23) [28]. The more severe neurologic deficits, e.g., obtundation and coma, usually are not seen until the P_{osm} exceeds 340 to 350 mosmol/kg (plasma glucose concentration greater than 700 to 800 mg/dl) [12,29]. In NKC, the plasma glucose concentration frequently is greater than 1000 mg/dl, and neurologic symptoms may be the reason that the patient seeks medical care. This degree of hyperglycemia is reached less often in DKA. This may be because patients with DKA seek medical care early with the symptoms of metabolic acidosis rather than late with those of hyperosmolality.

The symptoms produced by metabolic acidosis and hypovolemia have been presented in Chaps. 14 and 18. Circulatory insufficiency is not uncommon since the total fluid loss can average 8 to 10 liters in severe hyperglycemia [12].

DIAGNOSIS

The symptoms of polyuria, polydipsia, and weight loss plus the physical findings of volume depletion and perhaps hyperventilation and the odor of acetone on the patient's breath should suggest the presence of hyperglycemia with or without ketoacidosis. In addition, hyperglycemia (and hypoglycemia) should be included in the differential diagnosis of the comatose patient. Once suspected, the diagnosis can easily be confirmed by measuring the plasma glucose concentration, either in the laboratory or at the bedside with reagent sticks (Dextrostix). Glucosuria can be detected at this time with Clinitest tablets or Clinistix.

Ketonemia and ketonuria can be demonstrated by using nitroprusside tablets (Acetest) or reagent sticks (Ketostix). If, in a patient with metabolic acidosis, serum or plasma that is undiluted or diluted 1:1 with normal saline has a 4+ reaction for ketones, then ketoacidosis can be assumed to be present. It should be noted that nitroprusside measures acetoacetate and acetone but not β-hydroxybutyrate. The ratio of β-hydroxybutyrate to acetoacetate usually is 3:1 in DKA but may be as high as 8:1 with alcoholic ketoacidosis or when lactic acidosis coexists with DKA [30]. In these situations, nitroprusside can underestimate the severity of the ketoacidosis.

Hypoglycemic therapy with insulin should not be begun until the presence of hyperglycemia has been demonstrated. *The isolated finding of glucosuria or ketonemia does not necessarily mean that hyperglycemia is present, and the administration of insulin to such a patient may be dangerous* [31]. Diabetics, particularly those on insulin, can be in a coma due to hypoglycemia, e.g., due to too much insulin, rather than hyperglycemia. If the patient has not emptied his or her bladder for several hours, the urine may contain glucose, reflecting a period of hyperglycemia that may have existed several hours previously and not the current state. The administration of insulin in this setting will further reduce the plasma glucose concentration and can produce neurologic deterioration and death. Whenever there is a question as to the presence of hypoglycemia or hyperglycemia, it is always safer to give glucose (50 ml of 50% glucose intravenously) immediately after blood has been drawn for measurement of the plasma glucose concentration. This will dramatically improve the status of the hypoglycemic patient but will not be harmful to the patient with hyperglycemia.

In addition to diabetes mellitus, alcoholism can produce ketoacidosis [32]. In this condition, the plasma glucose concentration is less than 250 mg/dl and may be less than 100 mg/dl. The treatment of this disorder is to give glucose which will stimulate endogenous insulin secretion, resulting in the correction of the ketoacidosis. Since the plasma glucose concentration frequently is normal, the administration of exogenous insulin can precipitate severe hypoglycemia.

TREATMENT

Therapy must be directed toward each of the metabolic disturbances that may be present in the hyperglycemic patient: hyperosmolality, ketoacidosis, K^+ imbalance, and volume depletion. Since absolute or relative insulin deficiency is responsible for most of these problems, the administration of insulin and volume repletion are the mainstays of therapy. To assess the effect of treatment, the plasma glucose concentration should be measured every 2 h and the plasma electrolytes and arterial pH every 2 to 4 h until the patient is stable.

Insulin

Insulin acts to lower the plasma glucose concentration (and the P_{osm}), the plasma K^+ concentration, and to correct the ketoacidosis when present. A variety of different insulin regimens have been described, all using crystalline (regular) insulin, which have been effective in correcting these abnormalities [4,12,33–38]. Although it has been suggested that some patients with NKC may respond to extremely low doses of insulin, the average insulin requirement in NKC probably does not differ significantly from that in DKA [12].

Regular insulin can be given by the intravenous, subcutaneous, or intramuscular routes. When administered as an intravenous bolus, one is sure of the dose reaching the bloodstream, but the half-life of the insulin is only 4 to 5 min, and it is completely cleared from the plasma within 30 min [39]. Subcutaneous insulin begins to act within 30 min, reaching a peak effect at 2 to 3 h. Intramuscular insulin acts slightly faster than subcutaneous insulin. However, absorption from either of these sites may be erratic, particularly in patients with circulatory insufficiency, and late release of the insulin may result in hypoglycemia.

One regimen consists of an initial dose of insulin that is 10 percent of the plasma glucose concentration, for example, 100 units for a plasma glucose concentration of 1000 mg/dl [12]. Half of each dose is given intravenously and half subcutaneously (or alternatively the entire dose can be given intravenously). The plasma glucose concentration is measured every 2 h, either in the laboratory or with Dextrostix, and insulin again given as 10 percent of the plasma glucose concentration, for example, 60 units if the plasma glucose concentration has fallen to 600 mg/dl. The average insulin requirement using this protocol ranges from 200 to 400 units.

Studies have suggested that the plasma glucose concentration can be controlled with much lower doses of insulin (as little as 40 to 100 units) by the use of continuous intravenous infusions [33–38]. The infusion of 4 to 12 units of insulin per hour, after a similar loading dose given as an intravenous bolus, can lower the plasma glucose concentration by 65 to 125 mg/dl per hour, a rate that is similar to higher-dose regimens [36,37]. This suggests that the lower dose completely saturates the receptors affecting glucose metabolism in the liver and the skeletal muscle. This regimen also is effective in controlling the ketoacidosis although at a slightly slower rate than with higher doses [38]. To minimize insulin adsorption onto the glass and plastic tubing, relatively concentrated solutions should be used. For example, if 40 units of regular insulin is added to 100 ml of isotonic saline and given at the rate of 20 to 30 ml/h, the patient will receive 8 to 12 units per hour.

Either the high-dose or low-dose regimen is effective in controlling almost all patients with DKA or NKC. However, occasional patients display varying degrees of insulin resistance, as evidenced by the failure of the plasma glucose concentration to return toward normal. If this occurs, higher doses of insulin must be used in whatever dose is required to lower the plasma glucose concentration. This can be done by increasing the individual dose in the high-dose regimen or by increasing the concentration of insulin in the infusion and/or the rate of infusion in the low-dose protocol.

Rarely, patients die, apparently from cerebral edema, after therapy has been initiated [40,41]. Since the plasma glucose concentration does not fall much more than 100 mg/dl (about 5 mosmol) per hour, the cerebral edema is not due to a too rapid reduction in P_{osm}, as occurs in hypernatremia (see Chap. 23). Experiments have suggested that insulin itself may play an important role in the genesis of cerebral edema [42]. Lowering the plasma glucose concentration below 250 to 300 mg/dl in experimental diabetes with insulin can result in the generation of new osmoles (called idiogenic osmoles) within the brain cells. This increase in brain cell osmolality can draw water into the brain and produce cerebral edema. The importance of insulin in this phenomenon was suggested by the absence of idiogenic osmole formation when the plasma glucose concentration was reduced with peritoneal dialysis. Although this model has not been proved to be present in human hyperglycemia, it seems prudent to discontinue insulin and give dextrose-containing solutions, e.g., in half-isotonic saline, when the plasma glucose concentration falls below 300 mg/dl [12]. Further insulin therapy can be ordered according to fluctuations in the plasma glucose concentration or if ketoacidosis persists. Discontinuing insulin at this time also protects against the development of hypoglycemia and hypokalemia due to the administration of excessive amounts of insulin.

HCO_3^- and K^+

The problems of HCO_3^- and K^+ replacement in ketoacidosis have been discussed in detail in Chap. 18. Briefly stated, the administration of insulin enhances ketoacid utilization, resulting in the regeneration of HCO_3^- and spontaneous correction of the acidosis. Therefore, treatment with alkali should be restricted to patients with severe acidosis (arterial pH less than 7.15) and HCO_3^- given only in small doses sufficient to maintain the pH above 7.20 [43]. In the patient with normal respiratory compensation, this means raising the plasma HCO_3^- concentration to approximately 10 meq/l; this can usually be achieved with 50 to 100 meq of $NaHCO_3$. Overzealous use of HCO_3^- can result in a paradoxical fall in CSF pH and neurologic deterioration [44].

Acidosis causes K^+ to move out of the cells into the extracellular fluid. Although patients with DKA usually are total-body-K^+-depleted, e.g., because of renal losses (see page 220) and vomiting, this effect of acidosis may cause the initial plasma K^+ concentration to be elevated, occasionally to life-threatening levels. However, both the direct effect of insulin and the correction of the acidosis cause K^+ to move intracellularly and unmask the K^+ depletion. Once the plasma K^+ concentration falls below 5.0 meq/l, K^+ salts, either KCl or K_2HPO_4 [45], should be added to the intravenous infusions in a dose of 20 to 40 meq/l. Less than 5 percent of patients with DKA present with hypokalemia. This connotes a more dangerous degree of K^+ depletion, and K^+ replacement must be begun immediately at a rate of up to 40 meq/h (see Chap. 26) with careful monitoring of the plasma K^+ concentration, muscle strength, and the electrocardiogram.

Fluids

The average fluid loss is 8 to 10 liters in NKC (almost 25 percent of the total body water) [12] and somewhat less in DKA. With each liter of water, about 70 meq of monovalent cation, primarily Na^+, is lost. This reflects the enhanced water loss relative to solute induced by the glucose osmotic diuresis. In most cases, volume repletion can be achieved with half-isotonic saline (Na^+ concentration of 77 meq/l), a fluid similar in composition to that lost in the urine. When severe hypovolemia or shock is present, initial rehydration should be begun with isotonic saline (Na^+ concentration equal to 154 meq/l), which will still be hypotonic to plasma. In general, 4 to 5 liters of fluid is given in the first 12 h, with the remainder of the deficit replaced in the ensuing 24 to 36 h. If necessary, a central venous pressure catheter can be used to monitor the efficacy of volume repletion and to prevent overhydration.

PROBLEMS

24-1 A 33-year-old male insulin-dependent diabetic stops taking insulin for 2 days and is admitted to the hospital in an obtunded state. The following laboratory data are obtained:

$$\text{Plasma [glucose]} = 1180 \text{ mg/dl}$$
$$\text{Arterial pH} = 7.00$$
$$P_{CO_2} = 13$$
$$[HCO_3^-] = 3 \text{ meq/l}$$
$$[K^+] = 7.4$$
$$\text{Plasma ketones} = 4+, \text{ diluted } 1:2$$

The electrocardiogram reveals peaked T waves consistent with hyperkalemia. The diagnosis of diabetic ketoacidosis is made. The patient is given 50 units of regular insulin intravenously and 50 units subcutaneously and half-isotonic saline. Two hours later, the plasma glucose concentration is 1250 mg/dl.

(*a*) How much insulin would you order at this time?

(*b*) How would you have treated the hyperkalemia on admission?

24-2 A 66-year-old woman with maturity-onset diabetes controlled with tolbutamide and phenformin is brought to the emergency room. No other history is obtainable. On physical examination, the patient is found to be agitated, confused, and tachypneic. There are no signs of volume depletion. The laboratory data are:

Plasma $[Na^+] = 140$ meq/l	Arterial pH = 7.08
$[K^+] = 5.8$ meq/l	$P_{CO_2} = 12$ mmHg

$[Cl^-] = 105$ meq/l	Plasma ketones = 2+, undiluted
$[HCO_3^-] = 3$ meq/l	BUN = 60 mg/dl
[Glucose] = 198 mg/dl	[Creatinine] = 5.8 mg/dl

What is the most likely diagnosis? Which of the following would you give to the patient?
(*a*) Insulin.
(*b*) $NaHCO_3$.
(*c*) Half-isotonic saline.

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Interference of Icodextrin with Serum Amylase Activity Measurement.

Gerrit Schonicke, Bernd Grabensee, Jorg Plum. *Dept. of Nephrology and Rheumatology, Heinrich-Heine-University, Dusseldorf, NRW, Germany.*

Background: The Extraneal® solution, containing glucose polymer (Icodextrin) as an osmotic agent has gained a more widespread use in peritoneal dialysis in the last few years. Some small amounts of the original polymer as well as its hydrolyzed metabolites (maltose, maltotriose etc.) are found in the systemic circulation. After changing the PD-regime to a once daily use of icodextrin we found particularly low levels of serum amylase in some patients. This was even true in cases of clinically evident pancreatitis with high serum levels of lipase.

Methods: Five blood samples were obtained from different patients using a once daily exchange of icodextrin (Extraneal®). Four blood samples were obtained from patients using only glucose solution. All patients were free of clinical signs of pancreatitis. The amylase activity was measured by a routine laboratory method (Sigma No. 577) based upon the enzymatic cleavage of the oligosaccharide ET-G7PNP. Samples were supplemented with alpha-amylase from Merck (No.: 1.16312.0001) or various amounts of Extraneal® dialysate.

Results: Basal levels of serum amylase levels were significantly lower in patients using icodextrin compared to glucose exchanges (19.8 ± 3.8 U/l vs. 168.3 ± 24.4 U/l; $p < 0.001$). After adding alpha-amylase at a final concentration of 250 U/l recovery was significantly lower in icodextrin specimens compared to glucose specimens (37.4 ± 26.1 U/l ; recovery: 13.5 ± 8.7%, $p < 0.001$). When spiking icodextrin to serum samples from glucose patients there was a concentration dependent decrease in amylase activity.

Conclusion: The clinical routine method for measuring amylase activity uses a dye labeled oligosaccharide. The actual findings give evidence for the fact that icodextrin and/or its degradation products competitively interact as a substrate in the assay. Diagnostic errors may occur when relying on this assay system.

Cross-sectional Comparison of Malnutrition in Continuous Ambulatory Peritoneal Dialysis and Hemodialysis Patients

Bruno Cianciaruso, MD, Giuliano Brunori, MD, Joel D. Kopple, MD, Giacomo Traverso, MD, Giacomo Panarello, MD, Giuseppe Enia, MD, Paolo Strippoli, MD, Amedeo De Vecchi, MD, Mario Querques, MD, Giusto Viglino, MD, Edward Vonesh, PhD, and Rosario Maiorca, MD

● Although malnutrition is not uncommon in continuous ambulatory peritoneal dialysis (CAPD) and maintenance hemodialysis (MHD) patients, there has never been a large-scale comparison study of nutritional status with these two dialysis modalities. We therefore assessed protein-calorie nutrition in 224 CAPD patients and 263 MHD patients who were treated in eight centers in Italy. The CAPD patients were slightly older than the MHD patients (60.2 ± 14.2 years *v* 56.3 ± 15.1 years; *P* < 0.01), had undergone dialysis for less time (2.32 ± 2.10 years *v* 3.66 ± 2.66 years; *P* < 0.0001), and had higher residual renal function (1.83 ± 2.29 mL/min *v* 0.27 ± 0.91 mL/min; *P* < 0.0001). Protein nitrogen appearance was 60.5 ± 16.6 g/d and 61.9 ± 16.5 g/d in the CAPD and MHD patients, respectively. In CAPD versus MHD patients, serum total protein and albumin tended to be lower; serum transferrin and mid-arm muscle circumference were similar; and relative body weight, skinfold thickness, and estimated percent body fat tended to be greater. These greater values in CAPD patients were particularly evident in those who were 65 years of age or older. Serum glucose, total cholesterol, and triglycerides also were greater in CAPD patients. The subjective global nutritional assessment indicated a significantly greater proportion of malnourished CAPD patients than MHD patients (42.3% *v* 30.8%). The greater prevalence of malnutrition in CAPD patients diminished with age. Maintenance hemodialysis patients older than 76 years were more likely to be malnourished than CAPD patients. In patients less than 65 years of age, protein-calorie malnutrition was more likely to be present in CAPD patients than in MHD patients.

INDEX WORDS: Continuous ambulatory peritoneal dialysis; hemodialysis; protein-calorie malnutrition; nutritional status; subjective global nutritional assessment.

HEMODIALYSIS and peritoneal dialysis are now standard and accepted methods of renal replacement therapy for patients with end-stage renal disease. Both therapeutic modalities can promote long-term survival and rehabilitation. However, there is considerable debate as to whether these two types of dialysis are equally effective at preventing morbidity and mortality. A number of studies have compared the clinical response to maintenance hemodialysis (MHD) versus peritoneal dialysis.[1-12] In general, both therapeutic modalities are associated with a similar incidence of successful clinical outcome.[1-3,5-12] There has been only one study comparing the nutritional status of patients undergoing MHD versus patients treated with peritoneal dialysis.[13] The number of patients evaluated in this study was limited. The prevalence of malnutrition in MHD and peritoneal dialysis is an important issue because many reports indicate that protein malnutrition is a major risk factor for morbidity and mortality in chronic dialysis patients.[14-19]

We therefore carried out a multicenter clinical study comparing the nutritional status of MHD and continuous ambulatory peritoneal dialysis (CAPD) patients in Italy. Four hundred eighty seven patients from eight dialysis centers, distributed from Reggio Calabria in the South of Italy to Pordenone near the Austrian border, were studied. The results indicate that protein-calorie malnutrition occurs commonly in both MHD and CAPD patients. The risk of malnutrition may be somewhat greater in younger patients undergoing CAPD.

From Cattedre di Nefrologia Medica, Facolta' di Medicina, Universita' di Napoli, Universita' di Brescia, Divisioni di Nefrologia Ospedali "S. Martino" di Genova, Stabilimento Ospedaliero di Pordenone, Divisione "G. Monasterio" di Reggio Calabria, Ospedale "SS Annunziata" di Taranto, Centro Ospedaliero Croff di Milano, Ospedale Regionale di Foggia, and Ospedale "S. Lazzaro" di Alba, Italy; Baxter Healthcare Corporation, Round Lake, IL; and Harbor–UCLA Medical Center and UCLA, Torrance, CA.

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Address reprint requests to Bruno Cianciaruso, MD, Cattedra di Nefrologia Facolta' di Medicina, Universita' di Napoli, Via Pansini 5, 80131 Napoli, Italy.

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MATERIALS AND METHODS

Patients

Two hundred twenty-four CAPD patients and 263 MHD patients were assessed for protein-calorie malnutrition. Patients received dialysis therapy in eight public hospitals in the Italian National Health System. These hospitals were situated in Brescia, Genova, Pordenone, Reggio Calabria, Taranto, Milano, Foggia, and Alba. Inclusion criteria for the study included age of 18 years or older, chronic dialysis treatment for at least 3 months, and commencement of dialysis therapy after January 1981 (when CAPD first became widely established in Italy).

Exclusion criteria included a change in treatment modality from hemodialysis to peritoneal dialysis or vice versa, amputations above the elbow or below the knee, and hospitalization or peritonitis within the previous month. Since recruitment for this study was conducted over a period of 6 months, no patient was excluded because of hospitalization or peritonitis. All patients who were invited to enter the study agreed to participate. Thus, virtually every patient in the eight dialysis centers who satisfied the above eligibility criteria participated in the study.

Maintenance hemodialysis patients underwent dialysis three times weekly for approximately 4 hours, generally using a 1.0 to 1.5 m^2 surface area hollow fiber dialyzer made from cellulose (69.5%), cellulose acetate (5.1%), or noncellulosic membranes (25.4%). Blood flow was usually 280 to 300 mL/min and dialysate flow was usually 500 mL/min. Approximately 80% of CAPD patients performed four 2-L dialysis exchanges per day. The other 20% used less (ie, three) or more frequent (ie, five) exchanges each day. No patient underwent continuous cyclic peritoneal dialysis. No patient used less than 2-L exchanges. All CAPD patients used Y-shaped connectors. At the time of the study, 16% of CAPD patients and 34% of MHD patients were receiving regular injections of erythropoietin. Two percent of CAPD patients and 5% of MHD patients had received a renal transplant; they had recommenced treatment with their same maintenance dialysis modality at least 3 months previously.

Patients fasted from after dinner until the completion of their blood drawing (predialysis blood for MHD patients) the following day. On the day of the study, patients came to their dialysis unit with a 24-hour urine collection and, for the CAPD patients, the expended dialysate collected over the preceding 24 hours. The CAPD patients were examined after they had drained their overnight exchange and before the morning dialysate was instilled. Maintenance hemodialysis patients were evaluated immediately before the onset of their midweek hemodialysis treatment. All MHD patients received dialysis treatment in a morning or early afternoon shift; MHD patients undergoing dialysis in the early afternoon shift were allowed to eat a light snack of bread with lunch meat, but without cheese or other dairy products and with little or no sugar, 2 to 3 hours before their dialysis treatment.

Anthropometry, blood measurements, and subjective global nutritional assessment (SGNA)[20,21] were performed. All anthropometric measurements were performed according to Heymsfield et al[22] by a single investigator at each center. To minimize variability in the anthropometric measurements and the SGNA, the clinical investigators underwent a 2-hour training session by two instructors prior to the onset of the study on the techniques for performing these measurements. In addition, a video tape demonstrating the methods for anthropometry and SGNA by one of the instructors was given to the clinical investigators.

Body weight and skinfold measurements were taken with the abdomen empty of dialysate after overnight drainage in CAPD patients and posthemodialysis in all MHD patients. Relative body weight was calculated as the patient's edema-free weight multiplied by 100 and divided by the median weight of normal persons of the same age range, gender, height, and skeletal frame size as determined from the combined National Health and Nutritional Evaluation Surveys I and II data sets.[23,24] Desirable body weight was calculated as the patient's edema-free weight multiplied by 100 and divided by the median weight of normal persons with the greatest longevity and of similar gender, height, skeletal frame size, and approximate age range as determined from the 1983 Metropolitan Life Insurance Tables.[25] For calculation of relative and desirable body weights, frame size was estimated from the bicondylar breadth of the right elbow using a caliper or from the wrist circumference. The relative body weight is based on the median weights of the normal population. The desirable body weight is calculated from the median weights that are associated with the greatest longevity in normal American adults who have purchased life insurance. Relative body weight is used to assess the normalcy of an individuals body weight. Desirable body weight, since it is associated with greater longevity in normal individuals, is considered more desirable by some authors. The advantages and limitations of these two parameters are discussed in more detail elsewhere.[26] Values from North American individuals were used because we are not aware of such data from the Italian population. Since both relative and desirable body weight are adjusted for height, gender, age, and frame size, it seems reasonable to infer that these standards can be applied to these racial and ethnic groups.

Biceps, triceps (TSF), subscapular, and suprailiac skinfolds were measured with a Lange skinfold caliper (Cambridge Scientific Industries, Inc, Cambridge, MD).[22] Percent body fat was calculated from these four skinfold measurements according to the method of Durnin and Womersley.[27] Mid-arm circumference (MAC) was measured with a metal tape measure.[22] Mid-arm muscle circumference (MAMC) was derived as follows:

$$\text{MAMC} = \text{MAC} - \pi \cdot \text{TSF}$$

For MHD patients, MAC was measured in the arm that did not contain a functioning vascular access.

We modified the SGNA so that patients primarily were assessed by five criteria from the medical history (weight change, especially over the previous month; dietary intake, particularly over the previous 4 weeks; gastrointestinal symptoms, such as loss of appetite, anorexia, vomiting, and diarrhea; functional capacity of the patient; and underlying diseases, particularly as they may affect nutritional requirements) and two criteria from physical examination (subcutaneous fat mass, particularly in the triceps area and chest; and muscle wasting, especially in the quadriceps and shoulder girdle). Physicians performing the SGNA were not asked to look at the serum albumin or other biochemical parameters before rating the SGNA. However, since they were the primary care nephrologists for these patients, we cannot exclude that they knew or remembered the data from previous blood drawing. The SGNA initially included three categories: well-nourished, mildly/moderately malnourished, and severely malnourished. Few patients were severely malnourished, and the SGNA was usually classified as either normal or mild to severe malnutrition to increase the statistical power. Twenty-four hour urine and dialysate collections were obtained and analyzed for total protein, urea, and creatinine. Residual renal function was calculated as the mean of the urinary creatinine and urea clearances (milliliter per minute). To calculate the urinary clearances used, serum urea and creatinine were measured at the end of the urine collection for the CAPD patients and predialysis and postdialysis for the MHD patients. Kt/V_{urea} was estimated in hemodialysis patients from Daugirdas[28] as follows:

$$Kt/V_{urea} = -\ln (R - 0.03) + (4 - 3.5 * R) * UF/W$$

where R is the ratio of the postdialysis to predialysis plasma urea, UF is the ultrafiltration volume (liters) during dialysis, and W is the postdialysis weight (kilograms). In CAPD patients, Kt/V was calculated from the product of the dialysate outflow during a 24-hour period (Vd) and the average dialysate to plasma ratio of urea (D/P urea). For patients with residual renal function, the 24-hour urinary urea clearance, divided by V, was added to the Kt/V value. The volume of urea distribution (V) was considered equal to total body water and was estimated using the Watson equation.[29]

Protein nitrogen appearance (PNA), previously referred to as protein catabolic rate, was normalized to the patient's actual body weight (BW) and expressed in grams per kilogram per day. For CAPD patients PNA was calculated by a modification of the Gotch and Sargent method as follows[30]:

$$PNA = (9.35 * G) + (0.29 * BW * 0.58) + \text{dialysate protein (g)}$$

$$G = (\text{total UN in 24-hour urine} + \text{total UN in 24-hour effluent})$$

$$nPNA = PNA/BW$$

where UN is urea nitrogen and nPNA is normalized PNA. Normalized PNA was calculated in MHD patients according to the method of Sargent et al[31]:

$$PNA = (G + 1.7 + UUN)/0.154$$

$$G = \{[(5.8 * BW_t + (BW_{02} - BW_t) * 10] * C_{02} - 5.8 * BW_t * C_t\}/\text{interdialytic time (min)}$$

$$nPNA = PNA/BW_t$$

where BW_t is body weight at the end of the first dialysis, BW_{02} is body weight before the second dialysis, C_t is blood urea nitrogen at the end of first dialysis, C_{02} is predialysis blood urea nitrogen at the second dialysis, UUN is urea nitrogen concentration in urine collected during interdialytic interval, G is urea nitrogen appearance, and nPNA is the PNA normalized by dividing by the postdialysis body weight (BW_t).

All blood and urine chemistries were measured in the hospital clinical laboratory at the patient's dialysis center. Serum albumin was measured by the bromcresol green method in all centers. Total protein in peritoneal dialysate and in urine was analyzed with the biuret method.

Statistical Methods

The distributional properties of each of the response variables were evaluated for normality and possible outlying observations. Tests for normality were done for each variable within the categories of modality, sex, and nutritional status. If the percent of time that a variable failed normality exceeded 50%, then that variable was considered not to be normally distributed. Comparisons were performed using a two-sample *t*-test, a nonparametric Wilcoxon rank-sum test, or a Pearson's chi-square and Fisher's exact test. Pearson's chi-square and Fisher's exact test were done to compare CAPD and MHD for differences in percentage of patients having comorbid risk factors present. Logistic regression analysis was performed to evaluate the relationship between the probability of being malnourished and selected explanatory variables not used for SGNA (ie, age, sex). Data are expressed as mean $\pm$ SD. $P < 0.05$ was considered to be statistically significant.

RESULTS

Clinical characteristics of the patients are shown in Tables 1 and 2. Ages ranged from 21 to 91 years and 20 to 87 years in the CAPD and MHD patients, respectively. As illustrated in Table 1, in comparison to the CAPD patients, the individuals undergoing MHD on average were significantly younger (by 3.9 years; $P < 0.01$), had received dialysis therapy longer (by 1.34 years; $P < 0.001$), and had lower residual renal function (0.27 mL/min *v* 1.83 mL/min; $P < 0.001$). Both PNA and nPNA were similar in the two groups (Table 1). There was no difference in the distribution of renal diseases between the two groups, although there tended to be more cases of diabetic nephropathy (9% *v* 5%) and less instances of polycystic kidney disease (9% *v* 14%) in the CAPD patients. There was a higher incidence of coronary artery disease in the CAPD patients compared with the MHD patients, as diagnosed by electrocardiography ($P < 0.05$; Table 2). No other difference in the prevalence of comorbidity were observed between the two groups, although hepatic cirrhosis and diabetes mellitus tended to be more common in the CAPD patients.

Serum proteins and anthropometric measurements in men and woman are shown in Tables

Table 1. Patient Characteristics and Primary Renal Disease

	CAPD	MHD	Probability Value
No. of subjects (M/F)*	224 (124/100)	263 (155/108)	NS
Body weight (kg)†			
Male	70.6 ± 12.6	65.2 ± 10.6	<0.0001
Female	61.9 ± 12.3	56.0 ± 10.7	<0.001
Age (yr)	60.2 ± 14	56.3 ± 15	<0.01
Duration of dialysis (yr)	2.32 ± 2.1	3.66 ± 2.66	<0.0001
nPNA (g/kg/d)‡	0.94 ± 0.25	0.98 ± 0.22	NS
PNA (g/d)	60.5 ± 16.6	61.9 ± 16.5	NS
Estimated GFR (mL/min)‡§	1.83 ± 2.29	0.27 ± 0.91	<0.001
Weekly Kt/V‡	2.03 ± 0.75	4.08 ± 0.78	—
Urea nitrogen (mg/dL)	72 ± 20	81 ± 18	<0.0001
Cause of renal failure			
Glomerulonephritis	72 (35%)	85 (33%)	NS
Pyelonephritis	51 (25%)	64 (25%)	NS
Hypertensive nephrosclerosis	26 (13%)	37 (14%)	NS
Polycystic kidney disease	19 (9%)	36 (14%)	NS
Diabetic nephropathy	18 (9%)	13 (5%)	NS
Other	18 (9%)	21 (8%)	NS

NOTE. Data are given as mean values ± SD.
Abbreviations: GFR, glomerular filtration rate; NS, not significant.
* For some parameters data were available for less than these numbers of patients.
† Patients with evidence of edema or ascites were excluded from this analysis.
‡ Data were collected at the time of the patient examination for this study.
§ Mean of creatinine and urea clearance.

3 and 4. Because the CAPD patients were on average 4 years older, the data are shown for three age ranges as well as for all men or woman combined. For all men combined, serum total protein and albumin were significantly lower in CAPD patients than in MHD patients. Serum total protein also was lower in the CAPD patients than in the MHD patients aged 41 to 64 years. Serum albumin was lower in the male CAPD versus MHD patients in each age group. The relative and desirable body weights were greater in all male CAPD versus MHD patients as well as in some of the individual age brackets. Triceps and subscapular skinfold thickness and percent body fat were greater in all CAPD versus MHD patients as well as in one or two of the age groups.

Table 2. Major Comorbid Conditions

	CAPD (%)	MHD (%)	Probability Value
Coronary artery disease	46 (20.5)	32 (12.1)	<0.05
Non-ischemic cardiac disease	75 (33.4)	90 (34.2)	NS
Peripheral vascular disease	37 (16.5)	44 (16.7)	NS
Cerebrovascular disease	25 (11.1)	23 (8.7)	NS
Obstructive pulmonary disease	21 (9.3)	26 (9.8)	NS
Malignancy	9 (4.0)	13 (4.9)	NS
Cirrhosis of the liver	10 (4.4)	5 (1.9)	NS
Diabetes mellitus	18 (8.0)	13 (5.0)	NS
Insulin dependent	4 (2.0)	2 (0.8)	NS
Non-insulin-dependent	14 (6.3)	11 (4.2)	NS

Abbreviation: NS, not significant.

Among the female patients, serum total protein was only lower in the CAPD patients age 65 years or older (Table 4). Serum albumin was decreased in all CAPD versus MHD patients as well as in the CAPD patients in each age bracket. The relative and desirable body weights were greater in all female CAPD versus MHD patients; relative body weight also was greater in the female CAPD versus MHD patients aged 18 to 40 years old. Triceps and biceps skinfold thicknesses were increased in all CAPD versus MHD patients, and these skinfolds as well as the

Table 3. Serum Chemistries and Anthropometry Related to Nutritional Status in Men Undergoing Continuous Ambulatory Peritoneal Dialysis or Maintenance Hemodialysis

	Total			18–40 yr			41–64 yr			≥65 yr		
	CAPD	MHD	*P*	CAPD	MHD	*P*	CAPD	MHD	*P*	CAPD	MHD	*P*
No. of subjects	122	151	—	10	23	—	60	75	—	52	56	—
Age (yr)	60.0 ± 12	56.9 ± 15	NS	27.2 ± 10	31.6 ± 9	NS	55.7 ± 6	54.0 ± 7	NS	73.3 ± 5	71.7 ± 5	NS
nPNA (g/kg/d)	0.91 ± 0.25	0.95 ± 0.23	NS	0.87 ± 0.41	1.0 ± 0.33	NS	0.91 ± 0.27	0.96 ± 0.23	NS	0.88 ± 0.26	0.88 ± 0.24	NS
Total protein (g/dL)	6.6 ± 0.8	7.0 ± 0.5	<0.0001	6.9 ± 0.7	7.1 ± 0.6	NS	6.7 ± 0.7	7.0 ± 0.6	<0.01	6.5 ± 0.8	6.9 ± 0.5	NS
Albumin (g/dL)	3.7 ± 0.5	4.2 ± 0.5	<0.0001	4.0 ± 0.4	4.4 ± 0.4	<0.01	3.8 ± 0.5	4.2 ± 0.5	<0.0001	3.6 ± 0.5	4.0 ± 0.4	<0.0001
Transferrin (mg/dL)	253 ± 53	253 ± 67	NS	223 ± 38	217 ± 56	NS	261 ± 48	268 ± 66	NS	250 ± 59	249 ± 66	NS
RBW (%)	85 ± 12	80 ± 12	<0.01	85 ± 13	75 ± 9	<0.05	86 ± 14	82 ± 13	NS	85 ± 11	80 ± 10	<0.05
DBW (%)	95 ± 12	91 ± 12	<0.05	94 ± 17	87 ± 9	NS	94 ± 11	94 ± 14	NS	95 ± 12	89 ± 10	<0.01
MAMC (cm)	25 ± 3	24 ± 3	NS	24 ± 3	25 ± 3	NS	25 ± 3	24 ± 3	NS	24 ± 3	23 ± 2	NS
TSF (mm)	11 ± 5	9 ± 4	<0.01	10 ± 4	9 ± 5	NS	11 ± 6	9 ± 4	NS	10 ± 5	8 ± 3	<0.01
BSF (mm)	5.9 ± 3	5.2 ± 2	NS	4.7 ± 1.3	5.3 ± 3	NS	6.2 ± 4	5.3 ± 3	NS	5.8 ± 3	5.1 ± 2	NS
SSSF (mm)	14 ± 6	11 ± 5	<0.001	10 ± 4	11 ± 6	NS	14 ± 5	12 ± 5	<0.05	15 ± 6	11 ± 4	<0.001
SISF (mm)	11 ± 6	9 ± 5	NS	8 ± 2	9 ± 5	NS	11 ± 7	10 ± 6	NS	11 ± 6	8 ± 3	<0.05
BF (%)	22 ± 6	19 ± 6	<0.001	15 ± 4	16 ± 5	NS	22 ± 6	20 ± 6	<0.05	22 ± 6	19 ± 5	<0.01

Abbreviations: nPNA, protein nitrogen appearance normalized to patient's body weight; RBW, relative body weight; DBW, desired body weight; MAMC, mid-arm muscle circumference; TSF, triceps skinfold; BSF, biceps skinfold; SSSF, subscapular skinfold; SISF, suprailiac skinfold; BF, body fat; NS, not significant.

percent body fat were also increased in CAPD patients aged 65 years or older. Subscapular and suprailiac skinfolds were no different in any group of female CAPD versus MHD patients.

In men and women, considered separately, there was no difference in serum transferrin or midarm muscle circumference between all CAPD versus MHD patients or between CAPD versus MHD patients of any age bracket. Among the three age groups, in both men and women analysed separately, the lower serum proteins and the increased relative and desirable body weights, skinfold thicknesses, and percent body fat in the CAPD versus MHD patients were statistically significant, most often in individuals who were 65 years of age or older (Tables 3 and 4).

Since the SGNA gives a global or overall assessment of protein calorie nutritional status, we compared the SGNA in CAPD and MHD patients in greater detail (Table 5). For the CAPD patients, 57.7% were classified as well-nourished, 34.9% as mildly/moderately undernourished, and 7.4% as severely malnourished. For the MHD patients, 69.2% were classified as well-nourished, 26.6% as mildly/moderately malnourished, and 4.2% as severely malnourished. The CAPD patients had a significantly greater prevalence of malnutrition than the MHD patients (Fisher's exact test, $P = 0.025$). In both the CAPD or MHD groups analyzed separately, the proportion of men and women classified by SGNA as malnourished compared with normally nourished was similar. Since the CAPD patients were significantly older, the prevalence of malnutrition was re-examined after adjusting for age. The CAPD patients were malnourished more often than MHD patients among patients 41 to 64 years old ($n = 236$; $P < 0.035$). For patients 18 to 40 years old ($n = 56$), the difference did not reach statistical significance. For patients 65 years or older ($n = 186$), there was no difference in the SGNA between CAPD and MHD patients. Maintenance hemodialysis patients who were malnourished by the SGNA were significantly older than those classified as normally nourished (61.6 ± 14.4 years *v* 53.8 ± 14.8 years; $P < 0.0001$). In contrast, those CAPD patients classified by the SGNA as malnourished compared with normally nourished were not different in age (61.1 ± 15.5 years *v* 54.4 ± 13.0 years; P = NS). Figure 1 illustrates the relationship be-

Table 4. Serum Chemistries and Anthropometry Related to Nutritional Status in Women Undergoing Continuous Ambulatory Peritoneal Dialysis or Maintenance Hemodialysis

	Total			18-40 yr			41-64 yr			≥65 yr		
	CAPD	MHD	P	CAPD	MHD	P	CAPD	MHD	P	CAPD	MHD	P
No. of subjects	100	106	—	10	19	—	47	57	—	43	32	—
Age (yr)	59.9 ± 13	55.7 ± 15	NS	33.8 ± 6	30.2 ± 5.4	NS	53.2 ± 7	54.3 ± 6	NS	71.9 ± 5	71.6 ± 6	NS
nPNA (g/kg/d)	0.98 ± 0.26	1.01 ± 0.24	NS	1.01 ± 0.14	1.00 ± 0.30	NS	1.00 ± .031	1.02 ± 0.26	NS	0.90 ± 0.30	0.91 ± 0.28	NS
Total protein (g/dL)	6.7 ± 0.6	6.8 ± 0.5	NS	7.2 ± 0.7	6.9 ± 0.7	NS	6.8 ± 0.6	6.8 ± 0.5	NS	6.6 ± 0.6	6.9 ± 0.6	<0.05
Albumin (g/dL)	3.7 ± 0.5	4.1 ± 0.4	<0.0001	3.9 ± 0.4	4.3 ± 0.5	<0.05	3.8 ± 0.5	4.0 ± 0.4	<0.05	3.5 ± 0.4	4.1 ± 0.4	<0.0001
Transferrin (mg/dL)	256 ± 50	260 ± 75	NS	249 ± 30	228 ± 65	NS	255 ± 53	260 ± 67	NS	258 ± 52	277 ± 88	NS
RBW (%)	80 ± 15	75 ± 13	<0.05	79 ± 12	68 ± 8	<0.05	84 ± 17	78 ± 13	NS	75 ± 13	73 ± 12	NS
DBW (%)	100 ± 16	94 ± 115	<0.05	93 ± 17	84 ± 7	NS	103 ± 18	97 ± 16	NS	97 ± 14	93 ± 13	NS
MAMC (cm)	23 ± 3	22 ± 3	NS	20 ± 3	20 ± 3	NS	23 ± 4	23 ± 3	NS	22 ± 2	22 ± 3	NS
TSF (mm)	17 ± 8	15 ± 6	<0.05	13 ± 7	14 ± 5	NS	18 ± 8	17 ± 7	NS	17 ± 7	13 ± 5	<0.01
BSF (mm)	9.6 ± 5	7.7 ± 4	<0.01	7.0 ± 4	5.7 ± 2	NS	10.4 ± 6	9.1 ± 4	NS	9.2 ± 5	6.5 ± 3	<0.01
SSSF (mm)	16 ± 7	15 ± 7	NS	15 ± 10	10 ± 3	NS	16 ± 7	17 ± 8	NS	16 ± 7	13 ± 7	NS
SISF (mm)	12 ± 6	12 ± 6	NS	11 ± 7	10 ± 4	NS	13 ± 6	13 ± 6	NS	12 ± 5	12 ± 7	NS
BF (%)	33 ± 6	31 ± 6	NS	25 ± 7	25 ± 4	NS	33 ± 5	33 ± 5	NS	34 ± 5	31 ± 6	<0.05

Abbreviations: nPNA, protein nitrogen appearance normalized to patient's body weight; RBW, relative body weight; DBW, desirable body weight; MAMC, mid-arm muscle circumference; TSF, triceps skinfold; BSF, biceps skinfold; SSSF, subscapular skinfold; SISF, suprailiac skinfold; BF, body fat; NS, not significant.

tween the SGNA and age in men and women undergoing CAPD or MHD.

All CAPD patients combined had marginally greater muscle wasting, as assessed by the SGNA technique, than did the MHD patients; mild to severe muscle wasting was identified in 51.0% of CAPD patients and 38.6% of MHD patients ($P < 0.05$). Ankle edema was observed more commonly in CAPD patients (30.6%) than in MHD patients (12.4%) ($P < 0.0001$). When present, the ankle edema was usually in trace amounts. The assessment of body fat by the SGNA showed no significant difference in any group of CAPD patients versus hemodialysis subjects.

Table 5. Nutritional Status of Continuous Ambulatory Peritoneal Dialysis and Maintenance Hemodialysis Patients According to the Subjective Global Nutritional Assessment

	Total			18–40 yr			41–64 yr			≥65 yr		
	CAPD	MHD	P*	CAPD	MHD	P*	CAPD	MHD	P*	CAPD	MHD	P*
Total	215	263		16	40		103	133		96	90	
Normal nutrition	124 (57.7)	182 (69.2)	0.025	11 (68.7)	36 (90.0)	NS	63 (61.2)	102 (76.7)	0.035	50 (52.1)	44 (48.9)	NS
Mild moderate malnutrition	75 (34.9)	70 (26.6)		5 (31.3)	4 (10.0)		35 (34.0)	27 (20.3)		35 (36.5)	39 (43.3)	
Severe malnutrition	16 (7.4)	11 (4.2)		0	0		5 (4.8)	4 (3.0)		11 (11.5)	7 (7.8)	
Male	116	155		7	22		58	77		51	56	
Normal nutrition	67 (57.8)	105 (67.7)	NS	6 (85.7)	22 (100)	NS	33 (56.9)	56 (72.7)	NS	28 (54.9)	27 (48.2)	NS
Mild moderate malnutrition	39 (33.6)	42 (27.1)		1 (14.3)	0		22 (37.4)	18 (23.4)		16 (31.4)	24 (42.9)	
Severe malnutrition	10 (8.6)	8 (5.2)		0	0		3 (5.2)	3 (3.9)		7 (13.7)	5 (8.9)	
Female	99	108		9	18		45	56		45	34	
Normal nutrition	57 (57.6)	77 (71.3)	NS	5 (55.6)	14 (77.8)	NS	30 (66.7)	46 (82.1)	NS	22 (48.9)	17 (50.0)	NS
Mild moderate malnutrition	36 (36.4)	28 (25.9)		4 (44.4)	4 (22.2)		13 (28.9)	9 (16.1)		19 (42.2)	15 (44.1)	
Severe malnutrition	6 (6.1)	3 (2.8)		0	0		2 (4.4)	1 (1.8)		4 (8.9)	2 (5.9)	

NOTE. Numbers in parentheses indicate the percent of patients in this nutritional category.

Abbreviation: NS, not significant.

* Probability values for Fisher's exact test comparing the frequency distribution of SGNA between CAPD and MHD.

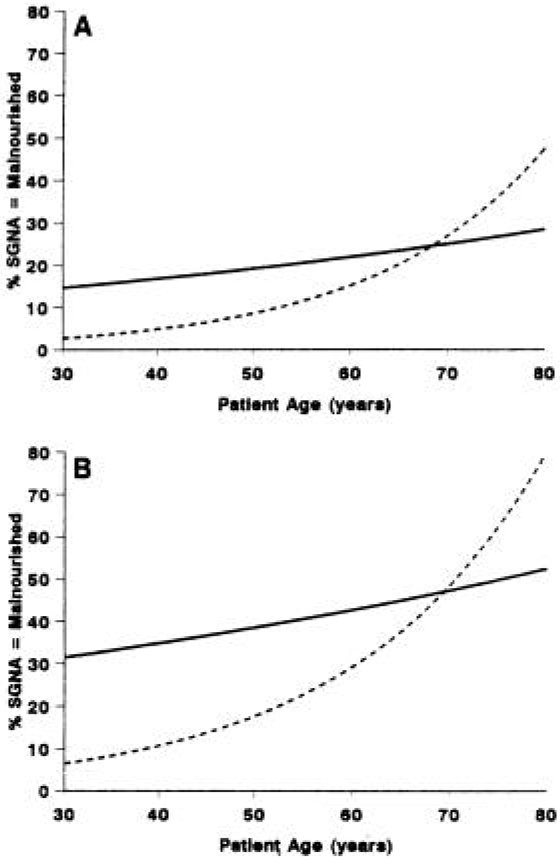

Fig 1. Relationship between the SGNA and age in men (A) and women (B) undergoing CAPD (solid line or MHD (broken line), as predicted from the logistic regression model.

The degree to which an abnormal SGNA reflected other parameters of protein-calorie malnutrition was also assessed for both CAPD and MHD patients classified as malnourished by the SGNA, as compared with those patients treated with the same dialysis modality who were classified as normally nourished. There was significantly lower serum total protein (CAPD, 6.5 $\pm$ 0.8 *v* 6.8 $\pm$ 0.6 g/dL, $P < 0.01$; MHD, 6.8 $\pm$ 0.6 *v* 7.0 $\pm$ 0.5 g/dL, $P < 0.05$), albumin (CAPD, 3.5 $\pm$ 0.5 *v* 3.8 $\pm$ 0.4 g/dL, $P < 0.0001$; MHD, 4.0 $\pm$ 0.5 *v* 4.2 $\pm$ 0.4 g/dL, $P < 0.0001$), and transferrin (CAPD, 245 $\pm$ 77 *v* 261 $\pm$ 66 mg/dL, $P < 0.05$; MHD, 245 $\pm$ 52 *v* 261 $\pm$ 50 mg/dL, $P < 0.05$), and relative and desirable body weights. Midarm muscle circumference, subscapular, triceps, biceps, and suprailiac skinfold thickness and the estimated percent body fat also were usually lower in the group of CAPD or MHD patients classified as malnourished by the SGNA. The skinfold thickness and proportion of body fat were more likely to be significantly reduced in the MHD rather than CAPD patients with an SGNA indicating malnutrition (data not shown). Patients designated as malnourished by the SGNA also had a significantly higher incidence of a recent decrease in food intake (CAPD or MHD patients; $P < 0.0001$). These results indicate that a low SGNA covaried with low visceral (ie, serum) protein concentrations, evidence for reduced somatic protein mass (ie, midarm muscle circumference), and body fat stores or energy intake. These data suggest that the SGNA technique appeared to give a global assessment of protein-calorie nutritional status.

The serum glucose, triglyceride, and total cholesterol concentrations were greater in all CAPD patients as well as in each of the three age brackets in comparison to the MHD patients; the only exception was the lack of significant difference in serum triglycerides in the CAPD versus MHD patients who were 41 to 64 years old (Table 6). Serum glucose was increased by 18% in the CAPD versus MHD patients. Both serum triglycerides and total cholesterol were 25 % higher in the CAPD versus MHD patients. There was no difference between CAPD and MHD in the total cohort of patients or in any age bracket with regard to serum low-density lipoprotein cholesterol or high-density lipoprotein cholesterol (Table 6).

There were no differences between the two groups with regard to the hemoglobin or hematocrit. However, the white blood cell count was significantly greater in the CAPD versus MHD patients in both men (8,010 $\pm$ 3,200 leukocytes/mm^3 *v* 6,370 $\pm$ 1,770 leukocytes/mm^3; $P < 0.0001$) and women (7,910 $\pm$ 2,380 leukocytes/mm^3 *v* 6,190 $\pm$ 1,870 leukocytes/mm^3; $P < 0.0001$).

DISCUSSION

To our knowledge, the present report describes the first large-scale comparison of the protein-calorie nutritional status of MHD versus CAPD patients. Each of the eight participating centers provided both MHD and CAPD for the study, and the dialysis centers were distributed over a

Table 6. Glucose and Lipid Profile in Continuous Ambulatory Peritoneal Ambulatory and Maintenance Dialysis Patients

	Total			18–40 yr			41–64 yr			≥65 yr		
	CAPD	MHD	*P*	CAPD	MHD	*P*	CAPD	MHD	*P*	CAPD	MHD	*P*
Glucose (mg/dL)	111 ± 43	94 ± 31	<0.0001	129 ± 74	89 ± 22	<0.01	107 ± 36	95 ± 37	<0.0001	110 ± 37	95 ± 22	<0.01
Triglycerides (mg/dL)	236 ± 148	188 ± 87	<0.01	225 ± 125	164 ± 68	<0.05	246 ± 162	199 ± 92	NS	227 ± 134	184 ± 84	<0.05
Total cholesterol (mg/dL)	228 ± 55	183 ± 47	<0.0001	242 ± 64	160 ± 38	<0.0001	223 ± 53	189 ± 44	<0.0001	231 ± 56	183 ± 52	<0.0001
LDL cholesterol (mg/dL)	171 ± 65	155 ± 57	NS	214 ± 45	116 ± 45	<0.01	154 ± 64	170 ± 53	NS	175 ± 66	150 ± 60	NS
HDL cholesterol (mg/dL)	38 ± 14	38 ± 13	NS	42 ± 13	37 ± 19	NS	35 ± 14	37 ± 10	NS	40 ± 13	38 ± 14	NS

NOTE. Data are given as mean values ± SD.
Abbreviations: LDL, low-density lipoprotein; HDL, high-density lipoprotein; NS, not significant.

wide geographic area on the Italian peninsula. Thus, the MHD and CAPD patients were from similar backgrounds and might be considered to represent typical Italian dialysis patients. The results of the present study indicate that protein-calorie malnutrition is common with both dialysis modalities.

A number of studies have previously examined the nutritional status of patients undergoing MHD or CAPD.[13,32-42] Virtually every published study has indicated that a substantial proportion of MHD and CAPD patients have protein-calorie malnutrition. The reported prevalence of protein-calorie malnutrition varies from 23% to 76% in MHD patients and from 18% to 56% in CAPD patients. However, only one study has compared the protein-calorie nutritional status in MHD patients with that of CAPD patients,[13] and no large-scale comparisons of the nutritional status of MHD and CAPD patients have been reported. Marckmann carried out such a comparison in 16 CAPD patients and 32 MHD patients who were treated in one dialysis center.[13] He reported that approximately 56% of CAPD patients and 37% of MHD patients had protein-calorie malnutrition. No significant differences in individual parameters of nutritional status were observed between the MHD and CAPD patients. Malnutrition tended to be more frequent during the first 12 months of dialysis therapy. Interpretation of the results of this study were complicated by the fact that the CAPD patients averaged 17 years older. O'Brien and Zimmerman described significantly higher serum cholesterol and lower serum albumin in 30 elderly chronic peritoneal dialysis patients compared with 31 elderly MHD patients.[43]

In the present study, the mean values for the nutritional measures and the prevalence of malnutrition, as estimated from the mean and standard deviation of these values, appeared to depend on the parameter used as the criterion of nutritional status. Serum total protein and albumin tended to be lower in the CAPD patients compared with the hemodialysis patients (Tables 3 and 4). Relative body weights, which express the patient's weight as a percentage of the median normal weight analyzed for age, gender, skeletal frame size, and height, were significantly reduced in both groups (normal values are 100%). However, both relative and desirable body weights were significantly lower in the MHD patients than in the CAPD patients. The greater body weights of the CAPD patients is probably at least partially due to the greater body fat of these individuals. Skinfold thickness tended to be greater in CAPD patients; in men and women aged 65 years or older and in men aged 41 to 64 years, body fat was increased in the individuals receiving CAPD. The fact that midarm muscle circumference was similar in CAPD versus MHD patients of either sex suggests that somatic or muscle protein mass was not different in the two groups.

The SGNA, which provides an overall assessment of nutritional status, indicated that protein-calorie malnutrition is more common in men and women undergoing CAPD and that it occurs in 42.3% of CAPD patients compared with 30.8% of MHD patients (Table 5; $P < 0.025$). This prevalence in the CAPD patients, 34.9% with mild to moderate malnutrition and 7.4% with severe malnutrition among those for whom gender status was identified (Table 5), is similar to the prevalence of malnutrition reported in a multicenter study of 224 chronic peritoneal dialysis patients carried out in six cities in North America and Europe.[42] In this latter study, using the SGNA as the criterion, 32.6% of chronic peritoneal dialysis patients had mild to moderate malnutrition and 8.0% had severe malnutrition.

Since the CAPD patients were significantly older than the MHD patients, by an average of 3.9 years, we also compared the nutritional status of the two groups according to each of three different age ranges. The mean and variance of the ages of the CAPD and MHD patients in each of these three groups were very similar or almost identical (Tables 3 and 4). Each age bracket of men or woman displayed lower serum albumin in the CAPD versus MHD patients. On the other hand, skinfold thicknesses and total body fat tended to be especially greater in the men and woman receiving CAPD versus MHD who were 65 years or older. The men undergoing CAPD who were aged 65 years or older were the only group to have both a greater relative body weight and desirable body weight than their MHD counterparts (Table 3). For the SGNA, this comparison indicated a significantly greater incidence of malnutrition in both men and woman undergoing CAPD compared with MHD who were aged 18 to 40 years or 41 to 64 years. However, the SGNA was not different in either men or women undergoing CAPD versus MHD who were 65 years or older (Table 5, Fig 1). These data suggest that the physician investigators relied more on body muscle mass, fat, and weight than on serum total protein or albumin to compare the SGNA in the CAPD versus MHD patients. However, within a given dialysis modality (ie, CAPD or MHD), we cannot exclude the possibility that serum albumin and possibly total protein and transferrin values might have influenced the classification of the SGNA (see Results).

Protein intake, as assessed from the PNA, was similar in the CAPD and MHD patients (Table 1). The body weight of the patients were slightly greater; this may reflect increased total body fat (Table 3 and 4) and possibly increased body water[44]; hence, the slightly lower protein intake in the CAPD patients compared with the MHD patients, when expressed as grams per kilogram body weight per day, may not indicate a more deficient protein intake in the former group. Nonetheless, in both CAPD and MHD patients, the dietary protein intake was often lower than is recommended.[45,46] This high incidence of reduced protein intake may be a cause for the protein malnutrition that was frequently detected in the current patients.

The greater weekly dialysate losses of protein, amino acids, and possibly peptides of the CAPD patients[43] may explain the lower serum total protein and albumin of these patients. It is noteworthy that serum transferrin was not different in the CAPD versus MHD patients. The clinical implications on patient outcome of a lower serum albumin in CAPD patients is not entirely clear. Lower serum albumin is associated with increased mortality in both CAPD and MHD patients.[16,19] The serum albumin below which the mortality rate begins to increase is approximately 3.9 to 4.0 g/dL in MHD patients.[16] The albumin concentrations at which mortality begins to increase in CAPD patients has not yet been well defined.[19]

The greater glucose uptake from dialysate and the consequent surge of serum insulin with the instillation of fresh dialysate-containing concentrated glucose[47] may explain the greater body fat and higher serum glucose, triglycerides, and total cholesterol in the CAPD patients.[48] It is possible that increased hepatic albumin synthesis to replace the daily albumin losses into the peritoneal dialysate also engenders the higher serum cholesterol levels in the CAPD patients compared with the MHD patients. Enhanced hepatic synthesis of albumin is believed to be associated with an increase in hepatic low-density lipoprotein cholesterol synthesis and serum total cholesterol levels.[49] Elevated serum triglycerides and total cholesterol in CAPD patients are well described.[50]

It is a cause for concern that the average serum cholesterol in the CAPD patients (228 ± 55 mg/dL) was above the upper limit of 200 mg/dL that has been recommended by the National Cholesterol Education Program of the National Heart, Lung, and Blood Institute.[51] It is noteworthy that serum low-density lipoprotein cholesterol was increased in both groups of patients to borderline high-risk levels.[50]

The finding that the prevalence of coronary artery disease was greater in the CAPD versus MHD patients may be related to the metabolic abnormalities of lipid metabolism in the CAPD patients. Although both CAPD and MHD patients displayed reduced high-density lipoprotein cholesterol and increased low-density lipoprotein cholesterol concentrations, serum glucose, triglycerides, and total cholesterol and, in men and older women, total body fat was greater in the CAPD patients compared with the MHD patients. Altered serum lipids and the increased body fat are known risk factors for vascular disease and mortality[52,53] in individuals who do not have advanced renal disease. These observations are consistent with the possibility that altered lipid metabolism and greater body fat of CAPD patients may place them at greater risk for vascular disease. However, an alternate possibility is that the patients that selected CAPD treatment had a higher incidence of coronary artery disease or a higher prevalence of risk factors predisposing to this disorder. Further research is clearly needed to examine these possibilities.

It should be emphasized that the patients in the present study were not assigned in a random fashion to CAPD or MHD. Hence, it is possible that bias in the selection of the treatment modality by the patient and health care team may have influenced the findings of this study. The observations that the primary renal disease (Table 1), comorbid conditions except for coronary artery disease (Table 2), and sex distribution between the CAPD and MHD patients were similar provide some evidence that if there was a selection bias operative in this study, it was not overwhelming. On the other hand, the findings of lower serum albumin, increased weight and body fat, similar serum transferrin and midarm muscle circumference, and elevated serum glucose, triglycerides, and total cholesterol in the CAPD versus MHD patients are consistent with a nutritional status profile in patients undergoing CAPD that is different from those receiving MHD.

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SYNOPSIS — RD-97-CA-130

<table>
<tr><td>Name of Company:
Baxter Healthcare Corporation</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier

Volume:

Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
7.5% Icodextrin Peritoneal Dialysis Solution</td></tr>
<tr><td>Name of Active Ingredient:
Icodextrin</td></tr>
</table>

<table>
<tr><td>Title of study:</td><td>A Study to Evaluate the Safety and Efficacy of a 7.5% Icodextrin Peritoneal Dialysis Solution in Patients Treated with Continuous Ambulatory Peritoneal Dialysis (CAPD)</td></tr>
<tr><td>Investigators and study centers:</td><td>See Appendix 16.1.4</td></tr>
<tr><td>Publication (reference):</td><td>Baxter Healthcare Corporation 2000: Document Number RD-97-CA-130</td></tr>
<tr><td>Studied period (years):</td><td>March 1998 – January 1999</td></tr>
<tr><td>Phase of development:</td><td>III</td></tr>
<tr><td>Objectives:</td><td>The purpose of this study was to evaluate the efficacy and safety of a peritoneal dialysis solution containing 7.5% Icodextrin as the long dwell exchange solution to replace the use of Dianeal® PD-2 or PD-4 Peritoneal Dialysis Solution with 2.5% dextrose in CAPD patients.</td></tr>
<tr><td>Methodology:</td><td>At least 144 evaluable patients were required for this prospective, randomized, double blind, parallel group, active-controlled study. Each center was asked to randomize approximately 6-8 patients. Patients participated in the study for 1 month (4 weeks).</td></tr>
<tr><td>Number of patients (planned and analyzed)</td><td>One hundred and seventy five patients entered the study as planned for an expected 20% dropout rate. Of these 175 patients, 163 completed the study and 12 patients discontinued the study.</td></tr>
<tr><td>Diagnosis and main criteria for inclusion:</td><td>Patients who met the following criteria participated in the study:
1. Patients who gave written informed consent.
2. Patients who were at least 18 years old.
3. Patients who were treated with CAPD for at least 90 days before the screening visit.
4. Patients whose standard prescription, for at least 30 days prior to the screening visit, included the following:
a. a long dwell for the night exchange of 12 ± 4 hours,
b. a long dwell for the night exchange with a fill volume of at least 2.0L but not greater than 2.5L of Dianeal® PD-2 or PD-4,
c. a long dwell with a concentration of 2.5% dextrose (2.27% glucose).
5. Patients who required a minimum of four peritoneal dialysis exchanges per 24-hour period (three daytime and one nighttime exchange) during the 30 days preceding the screening visit.</td></tr>
<tr><td>Test product:

Dose; lot number:

Mode of administration:</td><td>7.5% Icodextrin PD-2 Peritoneal Dialysis Solution with UltraBag™ or Twinbag configuration.

2.0L 7.5% Icodextrin PD-2; AX2020-C378414, JX0005-W8D06T1
2.5L 7.5% Icodextrin PD-2; AX2027-C380105, JX0008-W8D07T1

Administered intraperitoneally</td></tr>
<tr><td>Duration of treatment:</td><td>One exchange per day for the long dwell exchange.</td></tr>
</table>

Name of Company: Baxter Healthcare Corporation	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: 7.5% Icodextrin Peritoneal Dialysis Solution	**Volume:**	
Name of Active Ingredient: Icodextrin	**Page:**	

Control solution: Dose; lot number: Mode of administration:	2.0L or 2.5L Dianeal® PD-2 or PD-4 Peritoneal Dialysis Solution with 1.5% Dextrose in the UltraBag™ or Twinbag configuration. 2.0L Dianeal® PD-2 with 2.5% Dextrose; AX2022-C377846, JX0002-W8D08T0 2.5L Dianeal® PD-2 with 2.5% Dextrose; AX2028-C377853, JX0004-W8D08T1 Administered intraperitoneally
CRITERIA FOR EVALUATION:	
Efficacy:	The primary measure of efficacy was net ultrafiltration. Secondary measures of efficacy were peritoneal creatinine and urea nitrogen clearances.
Safety:	1. Complete review of all adverse events reported during the study especially with respect to the reported seriousness, severity, frequency, and possible relationship to the study solutions. 2. Total Icodextrin, maltose (DP_2), maltotriose (DP_3), maltotetraose (DP_4), maltopentaose (DP_5), maltohexaose (DP_6) and maltoheptaose (DP_7) plasma levels were measured at baseline and at the end of the study, to confirm that a steady state plasma level is reached. 3. Monitoring clinically meaningful changes from baseline: laboratory evaluations (hematology with differential, serum electrolytes, serum urea nitrogen, creatinine and liver enzymes), and fluid imbalances (i.e., edema, dehydration).
Statistical methods:	Repeated measures analysis of variance, analysis of covariance, Pearson's Chi-Square test, Fisher's exact test, Student t-test and Wilcoxon rank sum test. Statistical significance is defined as p < or = 0.05.
SUMMARY – CONCLUSIONS:	
Efficacy Results:	The primary efficacy variable was net ultrafiltration during the long dwell exchange. The Icodextrin treatment group had statistically significantly greater net UF for the long-dwell exchanges based on the repeated measures analysis. The mean difference in change from baseline between groups for net UF was 256.0 mL higher in the patients treated with Icodextrin as compared to Control patients. The secondary variables evaluated for efficacy were peritoneal creatinine clearance and peritoneal urea clearance during the long-dwell exchanges. As with the net UF, the creatinine and urea clearances statistically significantly greater for Icodextrin patients over Control patients. The study demonstrates that Icodextrin provided greater fluid removal (UF) and dialysis as compared to 2.5% dextrose during the long dwell. In addition, at Week 4, no patient in the Icodextrin Group had negative net ultrafiltration, in contrast to 13.4% of Control patients.

Name of Company: Baxter Healthcare Corporation	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: **7.5% Icodextrin Peritoneal Dialysis Solution**	**Volume:**	
Name of Active Ingredient: **Icodextrin**	**Page:**	

Safety Results:	There were a total of 424 adverse events (173 Control, 251 Icodextrin) reported by 135 patients (58 Control, 68.2%; 77 Icodextrin, 85.6%, p=0.006). These events occurred after study treatment initiation and through the follow-up period following the end of treatment administration. For the 58 Control patients reporting events, 21 (36.2%) reported at least one event judged to be at least possibly related to treatment. For the 77 Icodextrin patients reporting events, 33 (42.9%) reported at least one event judged to be at least possibly related to the treatment solution. There were 2 events that were discrepant between the groups. The events were RASH (1.2% Control, 12.2% Icodextrin) and DERM EXFOL (0.0% Control, and 5.6% Icodextrin). Serious adverse events were reported on 18 patients (9 Control, 9 Icodextrin). Ten patients (3 Control, 7 Icodextrin) discontinued from the study because of adverse events. There were no deaths reported during this study or during the follow-up period.
Conclusion:	The primary purpose of peritoneal dialysis solutions is excess water and waste solute removal. This study demonstrated that Icodextrin provided greater fluid removal (UF) and dialysis as compared to 2.5% dextrose during the long dwell. In addition, at Week 4, no patient in the Icodextrin Group had negative net ultrafiltration, in contrast to 13.4% of Control patients. This increase in net ultrafiltration is of benefit to patients treated with peritoneal dialysis who require increased fluid removal or who demonstrate negative ultrafiltration during the long dwell. While the overall adverse event rate was higher in the Icodextrin patients, there was no pattern of adverse events to relate this finding to Icodextrin. Furthermore, in other clinical studies with this product, the overall incidence for adverse events were comparable. It is concluded that Icodextrin was safe and well tolerated as a single long dwell exchange as part of the peritoneal dialysis prescription.
Date of the report:	September 28, 2000

SYNOPSIS — RD-97-CA-131

Name of sponsor company: **Baxter Healthcare Corporation**	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use Only)***
Name of finished product: **ExtranealÔ Peritoneal Dialysis Solution**	**Volume:**	
Name of active ingredient: **7.5% Icodextrin**	**Page:**	

Title of study:	A Study to Evaluate the Safety of a 7.5% Icodextrin Peritoneal Dialysis Solution in Patients Treated with Peritoneal Dialysis (PD) in North America.
Investigators and study centers:	A list of Principal Investigators and Study Sites are presented in Appendix 16.1.4.1.
Publication (reference):	Baxter Healthcare Corporation 2000: Document Number RD-97-CA-131
Studied period (years):	April 1998 – March 2000
Phase of development:	Phase III
Objectives:	The purpose of this study was to evaluate the safety of using a peritoneal dialysis solution containing 7.5% icodextrin as the long dwell solution to replace the current use of Dianeal® PD-2 or PD-4 Peritoneal Dialysis Solution with 2.5% Dextrose (2.27% glucose) in PD patients in North America.
Methodology:	Up to 300 patients were to be enrolled (at least 150 patients in the Icodextrin Treatment Group) in this prospective, randomized (2:1), double-blind, parallel-group, active-controlled study. Approximately 40 centers were expected to randomize at least six patients each. Patients were to participate in the study for 12 months (52 weeks).
Number of patients (planned and analyzed)	Two hundred eighty-seven (287) patients from 42 centers enrolled in this study. Of these 287 patients, 129 patients had also participated in the 1-month efficacy study. One hundred sixty-nine (169) patients completed the study and 118 patients withdrew from the study.
Diagnosis and main criteria for inclusion:	Patients who met the following criteria were offered the opportunity to participate in this study: 1. Patients who gave written informed consent. 2. Patients who were at least 18 years old. 3. Patients who had been treated with peritoneal dialysis (PD) for at least 90 days before the Screening Visit. 4. Patients whose standard prescription, for at least 30 days prior to the Screening Visit: a. included a long dwell of 12 ± 4 hours, b. included a long dwell with a fill volume of at least 2.0 L but not greater than 2.5 L of Dianeal® PD-2 or PD-4, c. included a long dwell with a concentration of 2.5% dextrose (2.27% glucose).

Name of sponsor company: Baxter Healthcare Corporation	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of finished product: ExtranealÔ Peritoneal Dialysis Solution	**Volume:**	
Name of active ingredient: 7.5% Icodextrin	**Page:**	

Test product: Dose; Batch No.; Product Code No.: Mode of administration:	Extraneal™ (7.5 icodextrin) Peritoneal Dialysis Solution 2.0 L and 2.5 L 7.5% icodextrin Peritoneal Dialysis Solution; Batch and product code numbers are provided in Appendix 16.1.6. Intraperitoneal
Duration of treatment:	One exchange per day for the long dwell exchange for 52 weeks.
Control solution: Dose; Batch No.; Product Code No.: Mode of administration:	Dianeal® Peritoneal Dialysis Solution with 2.5% Dextrose 2.0 L or 2.5 L Dianeal® PD-2 (patients in US) and PD-4 (patients in Canada) Peritoneal Dialysis Solution with 2.5% Dextrose; Batch and product code numbers are provided in Appendix 16.1.6. Intraperitoneal
CRITERIA FOR EVALUATION:	
Safety evaluations:	Safety was assessed by comparison of: mortality rates; changes from Baseline in membrane transport characteristics using the results of PET; incidence of adverse events; plasma levels for total icodextrin and metabolites; and clinically meaningful changes from Baseline for laboratory evaluations (hematology with differential, electrolytes, urea nitrogen, creatinine, liver enzymes), chest X-rays, fluid imbalances (i.e., weight, edema, dehydration), vital signs and physical examinations.
Statistical methods:	1. Mortality rates were assumed to occur with a Poisson rate over time within each treatment group. To establish the equivalence of the mortality rates between groups, a 90% confidence interval was constructed around the difference between the estimated Poisson means. 2. The PET variables were evaluated within each treatment group using paired t-tests to test for significant changes from Baseline and analysis of covariate to test for differences between treatment groups. The Baseline value was the covariate for each patient. 3. Adverse event rates, including serious adverse events, were compared using Pearson's Chi-Square tests (if the numbers were adequate) or Fisher's exact tests (if the numbers were sparse). 4. The plasma levels for total icodextrin, maltose (DP_2), maltotriose (DP_3), maltotetraose (DP_4), maltopentaose (DP_5), maltohexaose (DP_6), and maltoheptaose (DP_7), as collected over time, were evaluated by a) paired t-tests to compare each Follow-up time point to Baseline and b) repeated measures analyses to establish that the plasma levels reached a steady state and remained at those levels over time. 5. Clinically meaningful changes within each laboratory variable by Pearson's Chi-Square tests using normal ranges for ESRD patients.

Name of sponsor company: Baxter Healthcare Corporation	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of finished product: ExtranealÔ Peritoneal Dialysis Solution	Volume:	
Name of active ingredient: 7.5% Icodextrin	Page:	

SUMMARY – CONCLUSIONS:	
Safety results:	Mortality rates were comparable between treatment groups. There were no statistically significant differences between treatment groups for overall incidence, relatedness, severity or seriousness of adverse events. The incidence for "rash" was 7.3 percentage points greater for patients in the Icodextrin Group than for patients in the Control Group (11.6% Control and 18.9% Icodextrin). The incidence of "exfoliative dermatitis" was found to be 1.4 percentage points higher in the Icodextrin Group than in the Control Group (0.9% Control and 2.3% Icodextrin). Serious adverse events were reported by 143 patients (57, 51.4% Control and 86, 51.2% Icodextrin, p=1.000). The reason these events were classified as serious was most often due to hospitalization (49 Control and 70 Icodextrin). Some of the laboratory assays showed a trend in mean changes from baseline in the Icodextrin Group compared to the Control Group including mean decreases in sodium and chloride and mean increases in alkaline phosphatase. There were no clinically meaningful changes from baseline in findings for patients in either treatment group for physical examination, vital signs, or chest X-rays. For patients who completed both the Baseline and the Week 52 Kidney Disease Quality-of-Life (KDQoL) forms, there was a clinically meaningful difference favoring Icodextrin in 10 Symptom/Problem items while there was a clinically meaningful difference favoring Control in 5 Symptom/Problem items. There were no significant differences between treatment groups with regard to changes from Baseline to Week 52 scores for the eight SF-36 domains and two component summaries for those patients who completed both the Baseline and the Week 52 KDQoL questionnaires. However, there were clinically meaningful differences between treatment groups with regard to mean change in scores from Baseline to Week 52 favoring the Icodextrin Group for Role-Physical, Bodily Pain, General Health and Role-Emotional and favoring the Control Group for Vitality. When asked to compare their health in general now versus 1 year ago, a significantly greater (p=0.030) percentage of patients in the Icodextrin Group (30%) responded that their health was "much better now than 1 year ago" compared to patients in the Control Group (4%) for patients who completed both questionnaires.

Name of sponsor company: **Baxter Healthcare Corporation**	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use Only)***
Name of finished product: **ExtranealÔ Peritoneal Dialysis Solution**	**Volume:**	
Name of active ingredient: **7.5% Icodextrin**	**Page:**	

SUMMARY – CONCLUSIONS (continued):	
CONCLUSION:	This 12-month study demonstrates that icodextrin is safe and well tolerated as a peritoneal dialysis solution for the long dwell. The overall safety profile is similar to that of dextrose containing peritoneal dialysis solutions. Mortality and serious adverse events were not different between the patients who received Control and the patients who received Icodextrin PD solution. While several laboratory parameters changed in patients who were treated with Icodextrin, the observed changes were minor and did not cause clinical concern. Although exfoliative dermatitis and rash occurred more commonly in patients treated with Icodextrin as compared to patients treated with Control PD solution, overall skin disorders were similar between the two groups of patients.
Date of the report:	December 11, 2000

SYNOPSIS — ML/IB 001

Name of sponsor company: *9.4.1 ML Laboratories plc*	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use Only)***
Name of finished product: EXTRANEALÔ PERITONEAL DIALYSIS SOLUTION	**Volume:**	
Name of active ingredient: 7.5% icodextrin	**Page:**	

Title of study:	Multicentre Clinical Trial of Dextrin 20 in Continuous Ambulatory Peritoneal Dialysis (MIDAS)
Investigators and study centers:	The following eleven principal investigators participated in this study: Dr. R. Gokal, Manchester Royal infirmary, Manchester Dr. C. D. Mistry, Cardiff Royal Infirmary, Cardiff Dr. D. B. Brown, Northern General Hospital, Sheffield Dr. B. J. R. Junor, The Western Infirmary, Glasgow Dr. M. McMillan, Stobhill Hospital, Glasgow Dr. J. Michael, Queen Elizabeth Hospital, London Dr. M. Raftery, The London Hospital, London Dr. E. Clutterbuck, Hammersmith Hospital, London Prof. J. Walls, Leicester General Hospital, Leicester Dr. T. H. J. Goodship, Royal Victoria Infirmary, Newcastle Upon Tyne Prof. R. Wilkinson, Freeman Hospital, Newcastle Upon Tyne
Publication (reference):	ML Laboratories Final Clinical Study Report – ML/IB 001 1992.
Studied period (years):	March 1991 to February 1992
Phase of development:	**9.3 PHASE III**
Objectives:	The purpose of this study was to document the safety and tolerability of Dextrin 20 (7.5% icodextrin) compared with glucose (1.36%, 2.27% and 3.86%) peritoneal dialysis solution when used by CAPD patients for the long/overnight dwell in each 24 hours. Overnight dwells of 8 hours and 12 hours were evaluated.
Methodology:	This was a randomized, open-label, parallel-group, controlled study lasting 6 months and consisting of 12 clinic visits. Patients had a 12-hour overnight dwell at Weeks 4, 13, and 21.
Number of patients (planned and analyzed)	The MIDAS Study planned to enroll a 5% sample (200 patients) of the United Kingdom CAPD population. Actual enrollment included 209 patients from eleven hospitals (103 control and 106 icodextrin).
Diagnosis and main criteria for inclusion:	Inclusion Criteria included patients: 1. Aged 18 or over. 2. On CAPD for treatment of chronic renal failure for at least 3 months. 3. A daily treatment regimen consisting of 2 or 3 bags of 1.36% and 1 bag of 2.27% or 3.86% glucose OR 3 or 4 bags of 1.36% glucose solution. 4. Written informed consent given. 5. No CAPD-related abdominal pain or surgery for at least 1 month before randomization. 6. Using Baxter System 2 or Twin Bag System, or any Fresenius system.

Name of sponsor company: *9.4.2 ML Laboratories plc*	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of finished product: EXTRANEALÔ PERITONEAL DIALYSIS SOLUTION	**Volume:**	
Name of active ingredient: 7.5% icodextrin	**Page:**	

Test product: Dose; Batch No.; Product Code No.: Mode of administration:	Dextrin 20 (7.5% icodextrin) One 2.0 L bag/night; BCA32, AMB53 and BFA24 Intraperitoneal
Duration of treatment:	Nighttime, long dwell exchange (8 or 12 hours) daily for 6 months of treatment
Control solution: Dose; Batch No.; Product Code No.: Mode of administration:	Dianeal® Peritoneal Dialysis Solution (1.36%, 2.27% or 3.86% glucose) 1 or 2 bags/night of 1.5 L or 2.0 L solution Intraperitoneal
CRITERIA FOR EVALUATION:	
Efficacy evaluations:	The main efficacy assessment was the volume of ultrafiltrate produced by dialysis with icodextrin or control. On Weeks 4, 13 and 21 all patients had a 12-hour overnight dwell. Dialysis duration and the concentration of glucose bags used for the overnight exchange were recorded in patient diaries.
Safety evaluations:	Each patient's general health was assessed by continuous monitoring in a patient diary and by investigator assessment at each clinic visit. All changes in general health and treatment were recorded. Laboratory tests (including hematology, chemistry, liver function, lipids and carbohydrates) were performed at intervals throughout the study. Chest X-ray, ECG and slit-lamp eye examinations were performed.
Statistical methods:	Efficacy: Each patient's weekly median values for overnight ultrafiltration were compared by repeated measures analysis of variance on six patient subsets: low/weak (1.36%) or high/strong (2.27% and 3.86%) glucose concentrations, presence or absence of diabetes, and 1.5 or 2.0 L bag volumes. Paired t-tests were used to assess mean changes from run-in to particular specified weeks. Safety analyses included: • Weight and blood pressure measurements were summarized for each visit and for changes from visit 2. • Patients with and without CAPD symptoms were counted and the mean ± sd was calculated for each visit and for change from visit 2. Patient changes (worse, better, same) were counted and compared. • Exit site infection and peritonitis frequency was counted and graded at each visit including any resulting study withdrawals. • The number of normal/abnormal chest X-ray, ECG, and eye test reports at visits 2 and 12 were counted. • Creatinine clearance means for visits 2 and 12 and the difference between the visit means were calculated.

Name of sponsor company: *9.4.3 ML Laboratories plc*	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of finished product: EXTRANEAL Ô PERITONEAL DIALYSIS SOLUTION	**Volume:**	
Name of active ingredient: 7.5% icodextrin	**Page:**	

SUMMARY – CONCLUSIONS:

Efficacy results:

Overall adjusted mean changes from baseline in net ultrafiltration (mL) for 8-hr and 12-hr dwells for each treatment group follow:

Dwell	Control	Icodextrin	p-Value*
8-hr	29.22 mL	191.69 mL	<0.001
12-hr	-53.30 mL	242.43 mL	<0.001

*This p-Value from the two-sided test for treatment differences using the repeated measures analysis of covariance.

Adjusted mean changes from baseline in net ultrafiltration (mL) for 8- and 12-hr dwells for each treatment group by low and high glucose concentration subgroups follow:

Subgroup, Dwell	Control	Icodextrin	p-Value*
Low concentration (1.36% glucose/1.5% dextrose)			
8-hour	107.25 mL	429.59 mL	<0.001
12-hour	40.15 mL	479.02 mL	<0.001
High concentration (2.27%/3.86% glucose 2.5%/4.25% dextrose)			
8-hour	-86.27 mL	-200.15 mL	0.066
12-hour	-184.11 mL	-127.77 mL	0.455

*This p-Value from the two-sided test for treatment differences using the repeated measures analysis of covariance.

Name of sponsor company: *9.4.4 ML Laboratories plc*	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of finished product: EXTRANEALÔ PERITONEAL DIALYSIS SOLUTION	**Volume:**	
Name of active ingredient: 7.5% icodextrin	**Page:**	

Safety results:	Control patients gained weight and icodextrin patients lost weight during study participation. Blood pressure results remained stable for patients in both treatment groups throughout the study. Both treatment groups had similar results for evaluation of CAPD symptoms during treatment. There were similar reports of exit site infection for patients in both groups. Peritonitis rates were higher in the icodextrin group, consistent with a higher rate at study entry. Overall, the peritonitis rate was 1 per 13 patient-months. Two control patients expired during the study and one icodextrin patient expired one week after withdrawing from the study. Fifteen patients withdrew from the study (5 control, 10 icodextrin) due to adverse event(s). Of the 209 patients enrolled into this study, 171 patients reported at least one adverse event (84 control, 87 icodextrin). Fourteen patients reported serious adverse events (6 control, 8 icodextrin). There were no differences in laboratory variables between treatment groups during the study, except for slight decreases in sodium and chloride for patients in the icodextrin group and a slight increase in plasma osmolality for the icodextrin group. These changes were not considered clinically significant. Lipid profiles were similar between treatment groups at baseline, but tended to fall slightly for patients in the icodextrin group during the study.
CONCLUSION:	Icodextrin solution produced greater and more predictable UF than control solutions for all patient subgroups except the subgroup using strong/high glucose concentration solutions during an 8-hour dwell. Icodextrin solution remained well tolerated with only minor alterations in laboratory variables.

SYNOPSIS — PRO-RENAL-REG-035

Name of Company: **Baxter Healthcare Corporation**	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use Only)***
Name of Finished Product: 7.5% Icodextrin Peritoneal Dialysis Solution	**Volume:**	
Name of Active Ingredient: **Icodextrin**	**Page:**	

Title Of Study:	A Study To Evaluate The Safety And Efficacy Of A 7.5% Icodextrin Peritoneal Dialysis Solution In Patients Treated With Automated Peritoneal Dialysis (APD)
Protocol Number:	PRO-RENAL-REG-035
Study Phase”	Phase III
Objective:	The purpose of this study is to compare the safety and efficacy of a peritoneal dialysis solution containing 7.5% icodextrin as a long dwell exchange solution with the 2.27% glucose solution (Dianeal® PD4) in patients treated with APD.
Study Design:	At least 32 patients will be randomized into this prospective, randomized, open-label, parallel group, active-controlled study. With an expected drop out of 20%, approximately 40 patients will need to be enrolled. Each center (7 in total) will attempt to randomize about 6 patients. Patients will participate in the study for 4 months (16 weeks). The study will include a two week baseline period followed by a 12 week treatment period and finally a two week follow-up period.
Study Population:	Patients with End Stage Renal Disease (ESRD) being treated by automated peritoneal dialysis (APD) will be the study population.
Inclusion Criteria:	Patients meeting the following criteria will be offered the opportunity to participate in this study. 1. Patients who have given written informed consent. 2. Patients who are at least 18 years old. 3. Patients who have been treated with automated peritoneal dialysis (APD) for at least 90 days before the screening visit. 4. Patients whose standard prescription includes a long dwell daytime exchange of 14 $\pm$ 2 hours with 2 liter of 2.27% glucose PD4 and excludes any dry period / 24 h, 7 days a week during the 30 days preceding the screening visit.
Administration:	The control solution Dianeal® PD4 with a concentration of 2.27% glucose, and the test solution, 7.5% icodextrin, are administered intraperitoneally.
Visit Schedule:	Seven evaluation time points are scheduled during the 16 week study + 1 screening visit to determine patient eligibility.

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<tr><td>Name of Company:
Baxter Healthcare Corporation</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier

Volume:

Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
7.5% Icodextrin Peritoneal Dialysis Solution</td></tr>
<tr><td>Name of Active Ingredient:
Icodextrin</td></tr>
<tr><td colspan="3">Evaluation criteria:</td></tr>
<tr><td>Efficacy:</td><td colspan="2">The primary measure of efficacy will be net ultrafiltration. Secondary measures of efficacy will be peritoneal creatinine and urea clearances.</td></tr>
<tr><td>Safety:</td><td colspan="2">1. Peritoneal equilibration test (PET) will be performed during the baseline period and at the end of the treatment period. The data collected will be used to derive the mass transfer area coefficient (MTAC).

2. Carbohydrate absorption for the long dwell day exchange.

3. Complete review of all adverse events reported during the study especially with respect to the reported seriousness, severity, frequency and possible relationship to the study solutions.

4. Total icodextrin, maltose (DP_2), maltotriose (DP_3), maltotetraose (DP_4), maltopentaose (DP_5), maltohexaose (DP_6), and maltoheptaose (DP_7) plasma levels measured prior to, during, and after treatment in order to confirm that a steady state plasma level is reached and that levels return to baseline upon discontinuation of icodextrin (i.e., during the follow-up period).

5. Monitoring of clinically significant changes from baseline: routine laboratory evaluations (including hematology with differential, serum levels of electrolytes, urea, creatinine, and liver enzymes), fluid imbalances (i.e., edema, dehydration) and physical examinations.

6. Changes in insulin requirements for diabetic patients.

7. Clinically significant changes from baseline for laboratory values expected for dialysis patients.</td></tr>
<tr><td>Statistical Methods:</td><td colspan="2">Repeated measures analysis of variance, analysis of covariance, Fisher's exact test, Student t-test, and Wilcoxon rank sum test. Statistical significance is defined as $p \leq 0.05$.</td></tr>
</table>

SYNOPSIS — ML/IB 020

<table>
<tr><td>Name of sponsor company:
9.4.5 ML Laboratories plc</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier
Volume:

Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of finished product:
EXTRANEAL™ PERITONEAL DIALYSIS SOLUTION</td></tr>
<tr><td>Name of active ingredient:
7.5% icodextrin</td></tr>
</table>

Title of study:	Assessment of icodextrin for the long daytime dwell in automated peritoneal dialysis (APD) patients.
Investigators and study centers:	The Principal Investigator for this study was Dr. Iain Henderson at Ninewells Hospital in Dundee, United Kingdom.
Publication (reference):	ML Laboratories Final Clinical Study Report – ML/IB 020 1995.
Studied period (years):	December 1993 to December 1994
Phase of development:	**9.4 PHASE III**
Objectives:	The purpose of this study was to compare the safety, efficacy and acceptability of icodextrin for the long daytime dwell with that of a glucose solution in APD patients.
Methodology:	This was a randomized, open, 2-way crossover study consisting of a 2-week run in period, 6 weeks on the first treatment, a 4-week washout, and 6 weeks on the second treatment. All patients used their usual regimen (dry) for the long daytime dwell during the run in, washout and post study periods. There were eight clinic visits during the 20-week trial.
Number of patients (planned and analyzed)	Up to 20 patients were to be recruited for this study. Eleven patients were included in the statistical analysis for this study.
Diagnosis and main criteria for inclusion:	Inclusion Criteria included patients: 1. Aged 18 or over. 2. On APD for chronic renal failure for at least 1 month. 3. No peritonitis or related surgery for at least 1 month before visit 1. 4. Written informed consent given.
Test product: Dose; Batch No.; Product Code No.: Mode of administration:	Dextrin 20 (7.5% icodextrin) 2.0 L; 93I23G33; FPB5960R Intraperitoneal
Duration of treatment:	Daytime, long dwell exchange (14-16 hours) daily for each of the 6-week treatment periods.
Control solution: Dose; Batch No.; Product Code No.: Mode of administration:	Dianeal® Peritoneal Dialysis Solution with 4.25% Dextrose (3.86 glucose) 2.0 L; The control treatment used by all patients was actually a dry dwell. Intraperitoneal
CRITERIA FOR EVALUATION:	
Efficacy evaluations:	The main efficacy assessment was the volume of ultrafiltrate (UF) produced over 24 hours. Clearances of creatinine and urea (KT/V) were also assessed from the 24-hour urinary and PD fluid measurements.

Name of sponsor company: *9.4.6 ML Laboratories plc*	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of finished product: EXTRANEAL™ PERITONEAL DIALYSIS SOLUTION	**Volume:**	
Name of active ingredient: 7.5% icodextrin	**Page:**	

Safety evaluations:	The investigator assessed the patient's general health at each visit via a symptom list. All changes in health and medicines as well as laboratory test results were evaluated. Adverse events were also recorded.
Statistical methods:	Efficacy: Ultrafiltrate volumes were to be compared between treatment groups using an analysis of variance. The 24-hour PD measurements were tested using paired t-tests. Safety: Overall means on each treatment and changes from baseline were calculated for laboratory parameters. Symptom data were presented as a mean of the symptom score and changes calculated. Adverse events were listed by body system. Withdrawals and reasons for withdrawal were listed.
SUMMARY – CONCLUSIONS:	
Efficacy results:	Eleven patients were enrolled and seven patients completed the study. The groups were not comparable for UF volumes as all patients chose to remain dry during the day for the control period. The daytime icodextrin dwell resulted in UF volumes of 350 ± 230 mL (n=9) after 3 weeks and 390 ± 200 mL (n=7) after 6 weeks. Overall, there was little difference between the 24-hour totals achieved in the two treatment periods. There was a significantly greater ($p<0.01$) dialysis creatinine clearance during the icodextrin treatment period (47.4 ± 12.0 L/wk) as compared to the control period (29.5 ± 8.71 L/wk). The overall creatinine clearance was higher during the icodextrin treatment period (70.2 ± 16.9 L/wk) than the control treatment period (62.8 ± 12.4 L/wk), but not significantly ($p=0.07$). The total KT/V of urea was significantly greater ($p=0.04$) during the icodextrin period (2.20 ± 0.42) than the control period (1.83 ± 0.45).
Safety results:	The total symptom score was lower in the Icodextrin Treatment Period than the Control Period. There were no clinically significant changes in weight or blood pressure during the study. There were no clinically significant changes in hematology parameters or the majority of chemistry parameters during the study. Both sodium and chloride levels were significantly lower during the icodextrin treatment period compared to control ($p<0.05$). Urea, urate and creatinine were lower during icodextrin treatment. No patient deaths were reported during this study. Five of the eleven patients enrolled into the study experienced six serious adverse events during the treatment and follow-up periods of the study. There were two temporary and four permanent study withdrawals. Three of the four permanent withdrawals were due to peritonitis or other adverse events.

<table>
<tr><td>Name of sponsor company:
9.4.7 ML Laboratories plc</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier
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<tr><td>Name of finished product:
EXTRANEAL™ PERITONEAL DIALYSIS SOLUTION</td></tr>
<tr><td>Name of active ingredient:
7.5% icodextrin</td></tr>
</table>

CONCLUSION:	Icodextrin produces substantial ultrafiltration when used for the long daytime dwell in APD. This allows improved clearances and may permit improved flexibility in fluid intake or APD regime.

SYNOPSIS — ML/IB 011

Name of sponsor company: ***9.4.8 ML Laboratories plc***	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use Only)***
Name of finished product: EXTRANEAL™ PERITONEAL DIALYSIS SOLUTION	**Volume:**	
Name of active ingredient: 7.5% icodextrin	**Page:**	

Title of study:	Assessment of the biocompatibility of glucose polymer solution in Automated Peritoneal Dialysis (APD).
Investigators and study centers:	The Principal Investigator for this study was N. Posthuma, M.D., Dept. of Nephrology, Academisch Ziekenhuis Vrije Universiteit, The Netherlands.
Publication (reference):	ML Laboratories Final Clinical Study Report – ML/IB 011 1998.
Studied period (years):	January 1994 to May 1997
Phase of development:	**9.5 PHASE III**
Objectives:	The objectives of this study included comparison of icodextrin with glucose peritoneal dialysis solutions for use during the long daytime dwell in APD patients with regard to: safety and efficacy, damage to host resistance (macrophage function) and to the peritoneal membrane (transport, fibrosis, glycation), and glycation of peritoneal membrane proteins.
Methodology:	The DIANA study was a randomized, open-label, parallel-group comparison of icodextrin 7.5% solution with glucose solution for the long daytime dwell of 14 to 16 hours. The study treatment was intended to last for 2 years with study visits occurring every 3 months.
Number of patients (planned and analyzed)	Up to 40 patients were to be recruited for this study. It was originally intended that 20 patients would be already established on APD prior to study entry and the other 20 patients would be new to APD. Thirty-eight patients were actually randomized into the study, 19 per treatment group.
Diagnosis and main criteria for inclusion:	Inclusion Criteria included patients: 5. Currently on APD or requiring APD. 6. Written informed consent given. 7. Life expectancy of 2 years. 8. Stable clinical condition.
Test product: Dose; Batch No.; Product Code No.: Mode of administration:	Extraneal™ (7.5% icodextrin) Peritoneal Dialysis Solution 2.0 L; See section 1.5 of the Final Report, Test Drug(s)/Investigational Products. Intraperitoneal
Duration of treatment:	Daytime, long dwell exchange (14 to 16 hours) daily for 2 years.
Control product: Dose; Batch No.; Product Code No.: Mode of administration:	Dianeal® Peritoneal Dialysis Solution with 1.36, 2.27 or 3.86% glucose 2.0 or 5.0 L. Intraperitoneal

<table>
<tr><td>Name of sponsor company:
9.4.9 ML Laboratories plc</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier
Volume:

Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of finished product:
EXTRANEAL™ PERITONEAL DIALYSIS SOLUTION</td></tr>
<tr><td>Name of active ingredient:
7.5% icodextrin</td></tr>
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CRITERIA FOR EVALUATION:	
Efficacy evaluations:	The main efficacy assessment was ultrafiltration volume. Glucose load, urea and creatinine clearances and MTAC were secondary endpoints.
Safety evaluations:	Patients were asked to rate their general health at each visit using an APD symptoms list. Adverse events and patient withdrawals were recorded. All changes in health and medicines, as well as laboratory test results (chemistry, hematology, liver function, lipids) and vital signs (blood pressure and weight) were evaluated. Serum carbohydrate levels were measured. Samples were assessed for biocompatibility parameters.
Statistical methods:	An interim analysis was performed in July of 1995. Significance levels were reduced to 3% for the interim and final analyses, thus making the overall significance level 5%. Efficacy: Changes from baseline in ultrafiltration (UF) volumes were compared between groups using analysis of variance (ANOVA). Safety: The incidence of specific APD symptoms was recorded on a symptom-by-symptom basis. A total symptom score was calculated as the sum of the individual symptom scores – excluding the visual disturbance score. The mean values of laboratory measurements were tabulated with statistical testing restricted to sodium values, using repeated measures ANOVA to compare groups. No statistical testing of osmolality or chloride levels were performed due to the small number of values available. Peritonitis, exit site infection, catheter-related events, adverse events and withdrawals were presented on a case-by-case basis and a summary table was provided. Patient weights were compared using ANOVA to determine any between group differences.
SUMMARY – CONCLUSIONS:	
Efficacy results:	At baseline, daytime UF volumes for both treatment groups were negative, i.e., both groups were reabsorbing fluid when using glucose for the long daytime dwell. The pattern of fluid reabsorption during the daytime dwell continued throughout most of the study for patients in the glucose group, but UF volumes increased to a mean of 218 mL at 3 months and a mean of 233 mL at 24 months for patients in the icodextrin group. Although the supplementary UF generated by icodextrin appeared gradually to fall over the study period, the overall increase remained statistically significant (p<0.001). The MTAC for urea and creatinine were stable and appeared unaffected by the control or test treatment.

Name of sponsor company: *9.4.10 ML Laboratories plc*	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use Only)***
Name of finished product: EXTRANEAL™ PERITONEAL DIALYSIS SOLUTION	**Volume:**	
Name of active ingredient: 7.5% icodextrin	**Page:**	

SUMMARY – CONCLUSIONS, continued:	
Safety results:	There was little apparent change in the pattern of symptom incidence over the study period in either treatment group. Five patients in the control group died during participation in the study and one patient, also from the control group, died two-and-one-half months after participating in the study. Thirty-four patients experienced at least one adverse event during this study (15 control and 19 icodextrin). Twenty-one patients experienced 48 serious adverse events (12 control patients had 27 serious adverse events, 9 icodextrin patients had 21 serious adverse events). Six patients in the control group and one patient in the icodextrin group permanently withdrew from the study due to peritonitis or other adverse events. Most of the biochemistry parameters remained stable throughout the study, with no differences between treatment groups. The exceptions were: sodium values decreased at 3 months compared to baseline in the icodextrin group, but did not decrease further over the life of the study and the changes were not significantly different between groups at any time point; chloride levels fell in the icodextrin group within the first 6 months and then stabilized; glucose levels were generally lower in the icodextrin group compared to the control group, but there was large inter-patient variability. Lipid and glycated hemoglobin values remained stable in both groups over the study period. Rates of peritonitis and exit site infection were similar in both groups. There was also no difference in biocompatibility parameters between the two treatment groups.
CONCLUSION:	This study showed that the use of icodextrin for the long daytime dwell in APD patients led to an increase in UF of at least 200 mL per day, which was maintained over at least 24 months, compared to patients in the control group who continued fluid reabsorption throughout the study. Icodextrin was found to be well tolerated with no effect on residual renal function or function of the peritoneal membrane.

Name of sponsor company: ***9.4.11 ML Laboratories plc***	**Individual Study Table Referring to Part of the Dossier Volume:**	***(For National Authority Use Only)***
Name of finished product: EXTRANEALÔ PERITONEAL DIALYSIS SOLUTION		
Name of active ingredient: 7.5% icodextrin	**Page:**	

Title of study:	Multicentre Clinical Study of Icodextrin in Continuous Ambulatory Peritoneal Dialysis: Extension Study
Investigators and study centers:	The following eight principal investigators participated in this study: Dr. R. Gokal, Manchester Royal infirmary, Manchester Dr. C. D. Mistry, Cardiff Royal Infirmary, Cardiff Dr. D. B. Brown, Northern General Hospital, Sheffield Dr. J. Michael, Queen Elizabeth Hospital, London Dr. M. J. Raftery, The Royal London Hospital, London Dr. E. Clutterbuck, Hammersmith Hospital, London Prof. J. Walls, Leicester General Hospital, Leicester Prof. R. Wilkinson, Freeman Hospital, Newcastle Upon Tyne
Publication (reference):	ML Laboratories Final Clinical Study Report – ML/IB 004 1995
Studied period (years):	October 1991 to February 1995
Phase of development:	**9.6 PHASE III**
Objectives:	The objectives of the MIDAS-2 study were to assess the continued safety of icodextrin for the long dwell in CAPD patients who had already received icodextrin for 6 months and who wished to continue receiving icodextrin.
Methodology:	Open, controlled study of 6-month continuation of treatment with icodextrin solution for the overnight dwell (all patients received icodextrin). Patients were allowed to enter the study from October 1991 as they completed the MIDAS study.
Number of patients (planned and analyzed)	Eight of the original eleven sites from the MIDAS study had patients who wished to continue icodextrin treatment in the MIDAS-2 study. Of the 61 available patients who completed the MIDAS study at these sites, 48 patients were enrolled in the MIDAS-2 study.
Diagnosis and main criteria for inclusion:	Inclusion criteria included: 1. Previous participation in and completion of the MIDAS study, for which inclusion criteria were as follows: • Aged 18 or over. • Received CAPD treatment for at least 3 months. • Previous regimen of 3 or 4 bags of 1.36% glucose and 0 or 1 bag of 3.86% glucose solution. • No CAPD-related abdominal pain or surgery in month. • Using Baxter system 2 or solo or Fresenius ANDY systems. 2. Investigator considered it beneficial for patient to continue icodextrin. 3. Written informed consent given.

Name of sponsor company: ***9.4.12 ML Laboratories plc***	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use Only)***
Name of finished product: **EXTRANEALÔ PERITONEAL DIALYSIS SOLUTION**	**Volume:**	
Name of active ingredient: 7.5% icodextrin	**Page:**	

Test product: Dose; Batch/Product Code No.: Mode of administration:	Dextrin 20 (7.5% icodextrin) Peritoneal Dialysis Solution One 1.5 L or 2.0 L bag per overnight dwell; Batch numbers are provided in the clinical study report. Intraperitoneal
Duration of treatment:	Continuation of treatment in 6-month intervals
Control solution: Dose; Batch/Product Code No.: Mode of administration:	No control solution was used in this study.
CRITERIA FOR EVALUATION:	
Efficacy evaluations:	Efficacy evaluations were not a primary aim of the MIDAS-2 study.
Safety evaluations:	General health and progress were assessed at the patient's usual outpatient visits for CAPD treatment (every 3 to 6 months). Blood pressure, weight, CAPD symptoms, adverse events, peritonitis and exit site infections, chemistry and hematology safety laboratory testing, serum carbohydrate measurement for the estimation of icodextrin and metabolites and eye examinations (slit-lamp) data were collected routinely throughout the study.
Statistical methods:	Descriptive statistics were used for all data. Weight, blood pressure, overall well being and laboratory values were expressed as means ± standard deviation. The percentages of patients with each symptom were recorded for specific CAPD symptoms.
SUMMARY – CONCLUSIONS:	
Efficacy results:	No efficacy parameters were assessed in this study.
Safety results:	There were no significant changes in body weight or blood pressure during icodextrin treatment. Mean blood pressure values suggested that blood pressure was well controlled with values maintained around 140/80 mmHg. Hematology values remained stable over 42 months on icodextrin. Sodium values fell by approximately 3 mmol/L on starting icodextrin and remained constant up to 42 months treatment. Potassium and phosphate showed a slight tendency to increase over 30 months while osmolality remained stable and chloride fell slightly. Forty-two patients reported adverse events and eighteen patients reported serious adverse events during participation in this study. Table 8 of the April 1995 ML Laboratories Clinical Study Report noted deaths for thirteen patients during or following icodextrin treatment. Patient #0719, who expired after 1781 days in the study, was not included in the ML Laboratories' report. Deaths of Patients #0961 and #1202 occurred two months after withdrawal from the study and were not included in Baxter tables. Nineteen patients withdrew from the study due to adverse events.

Name of sponsor company: *9.4.13 ML Laboratories plc*	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use Only)***
Name of finished product: EXTRANEALÔ PERITONEAL DIALYSIS SOLUTION	**Volume:**	
Name of active ingredient: 7.5% icodextrin	**Page:**	

Safety results, continued:	From the start of the original MIDAS study up to February of 1995, a mean of 0.1 ± 1.6 episodes of peritonitis were reported by 19 patients over a period of 23.6 ± 11.1 months for a rate of approximately 1 episode of peritonitis per 25 months. There were 11 cases of exit site infection reported in eight patients, 1 tunnel infection, 1 tube change due to peritonitis, and 5 reports of cloudy bags with no other symptoms reported by two patients. There was no evidence of accumulation of maltose or total carbohydrate over 30 months of icodextrin treatment. Most CAPD symptoms declined on starting icodextrin and remained lessened throughout treatment on icodextrin. One diabetic patient was referred for the removal of cataract. There were no changes or other outstanding findings on eye examinations.
CONCLUSION:	Icodextrin continued to be well tolerated in CAPD patients up to 3.5 years after starting treatment.

SYNOPSIS — RD-99-CA-060

Name of Company: **Baxter Healthcare Corporation**	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use Only)***
Name of Finished Product: **7.5% Icodextrin Peritoneal Dialysis Solution**	**Volume:**	
Name of Active Ingredient: **Icodextrin**	**Page:**	

Protocol Number:	RD-99-CA-060
Title of Study:	A Study to Evaluate the Pharmacokinetics of a single exchange of 7.5% Icodextrin Peritoneal Dialysis Solution in Patients Treated with Peritoneal Dialysis
Study Phase:	Phase I
Objective:	The purpose of this study is to evaluate the pharmacokinetics upon administration of a single exchange of 7.5% icodextrin peritoneal dialysis solution in PD patients.
Study Design:	An estimated 15 patients will be enrolled in this prospective study, for an estimated 10 patients completing the study. Patients will participate in the study for 4 weeks.
Study Population:	Patients with End Stage Renal Disease (ESRD) being treated with peritoneal dialysis.
Inclusion Criteria:	Patients meeting the following criteria will be offered the opportunity to participate in this study: 1. Patients who have given written informed consent. 2. Patients who are at least 18 years old. 3. Patients who have been treated with peritoneal dialysis (PD) for at least 90 days preceding Screening. 4. Patients who require at least four exchanges daily 5. Patients whose standard prescription for at least 30 days preceding Screening: a. has a typical fill volume of 2.0L or 2.5L of Dianeal® PD-2 or PD-4; b. includes a long dwell of 8-16 hours with a fill volume of 2.0 L or 2.5 L 6. Patients who have a residual renal function of ≤ 10 cc/minute as recorded in their medical record within 6 months preceding Screening.
Administration:	The test solution, 7.5% icodextrin peritoneal dialysis solution, will be administered intraperitoneally.
Visit Schedule:	There will be a total of six visits during this four-week study. The patient will provide informed consent at Screening. Visit 0 (Baseline) will occur within 14 days of Screening and will be a 24-hour inpatient visit, followed by four outpatient visits at Day 3, Day 7, Day 14 and Day 28.

Name of Company: Baxter Healthcare Corporation	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: 7.5% Icodextrin Peritoneal Dialysis Solution	**Volume:**	
Name of Active Ingredient: Icodextrin	**Page:**	

Evaluation Criteria	
Pharmacokinetics:	The absorption and elimination of icodextrin will be determined by the measurement of icodextrin and primary icodextrin metabolites in plasma, dialysate and urine upon administration of a single 12 hour icodextrin exchange. Blood samples will be collected for analysis at Baseline and at time 2, 4, 8, 12, 16, 24 hours, and Days 3, 7, 14 and 28. Dialysate samples will be collected at 0, 2, 4, 8 and 12 hours during the study solution exchange, ten minutes after the first post-study dwell is instilled and at the end of each of the non-icodextrin dialysis exchanges during the first 24 hours (e.g., 16, 20 and 24 hours). Urine will be collected for analysis during the first 24 hours of the study.
Safety:	1. Complete review of all adverse events reported during the study, especially with respect to the reported seriousness, severity, frequency, and possible relationship to the study solution. 2. Monitoring clinically meaningful changes from Baseline: laboratory evaluations (hematology with differential, serum electrolytes, serum urea nitrogen, creatinine, and liver enzymes), fluid imbalances (i.e., weight changes, edema, dehydration) and physical examinations.
Statistical:	The pharmacokinetic analysis will be performed on icodextrin plasma concentration-time data to estimate the clearance rate, the absorption rate constant, the elimination rate constant, C_{max}, T_{max}, and AUC. Appropriate kinetic analysis will be performed on the primary metabolites of icodextrin. For safety, the adverse events for this study will be summarized by incidence rates for which each patient is counted once for each event that he or she reported and total frequencies reported, by severity of event. In addition, a complete listing of all adverse events reported will be provided. The events will be categorized by COSTART body system and COSTART preferred term in all analyses. Changes from baseline will be calculated for each lab assay at each follow-up time point and the means and mean changes at each visit (Days 3, 7, 14 and 28) will be calculated. The standard error, minimum, and maximum will also be displayed as well as a test for significance for the mean change from baseline. The mean changes will be assessed for clinical relevance as well as statistical significance.

Name of sponsor company: *9.4.14 ML Laboratories plc*	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of finished product: EXTRANEALÔ PERITONEAL DIALYSIS SOLUTION	**Volume:**	
Name of active ingredient: 7.5% icodextrin	**Page:**	

Title of study:	Evaluation of Serum Levels of Icodextrin at Steady State, After Stopping Treatment and on Re-Starting After Three Weeks
Investigators and study centers:	The Principal Investigators for this study were M. J. Raftery, MD, MRCP, at Royal London Hospital, Whitechapel, London, and Professor J. Walls, MD, FRCP, Leicester General Hospital, Leicester.
Publication (reference):	ML Laboratories Final Clinical Study Report – ML/IB 014 1995.
Studied period (years):	February 1993 to May 1993
Phase of development:	**9.7 PHASE I**
Objectives:	The aim of this steady-state, stop, start study (S5) was to measure icodextrin and metabolite levels after ceasing icodextrin treatment, after 2 years of icodextrin treatment, and on re-start of icodextrin.
Methodology:	This was a randomized, open-label, multi-center, parallel-group substudy of the MIDAS-2 study. CAPD patients from the MIDAS-2 study who had received icodextrin for the overnight dwell for up to 18 months participated in the S5 study (3 weeks on glucose followed by 2 weeks on icodextrin). Four study site visits were performed during this study.
Number of patients (planned and analyzed)	Ten patients were needed to complete the study. A total of 12 patients were enrolled into the study, 5 from London and 7 from Leicester.
Diagnosis and main criteria for inclusion:	Inclusion Criteria consisted of patients who were in MIDAS-2 and patients who had given informed consent.
Test product: Dose; Batch No.; Product Code No.: Mode of administration:	Dextrin 20 (7.5% icodextrin) 1 bag/night Intraperitoneal
Duration of treatment:	Nighttime, long dwell exchange once daily for 3 weeks with glucose followed by 2 weeks with icodextrin peritoneal dialysis solution.
Control solution: Dose; Batch No.; Product Code No.: Mode of administration:	Dianeal® Peritoneal Dialysis Solution with 1.36% or 3.86% glucose 1 bag/night Intraperitoneal
CRITERIA FOR EVALUATION:	
Efficacy evaluations:	Serum levels of icodextrin and metabolites were assessed pre-MIDAS (prior to ever receiving icodextrin), after 2 years of icodextrin treatment (at Day 1 of the S5 study, i.e., steady state), during the 3 weeks off icodextrin treatment, and during the 2 weeks after re-starting icodextrin. Ultrafiltration volumes were also collected weekly throughout the study.

Name of sponsor company: *9.4.15 ML Laboratories plc*	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of finished product: EXTRANEALÔ PERITONEAL DIALYSIS SOLUTION	**Volume:**	
Name of active ingredient: 7.5% icodextrin	**Page:**	

Safety evaluations:	Changes in health or medications, adverse events, blood pressure, weight and CAPD symptoms were recorded. Blood samples for safety laboratory testing were collected at each visit.
Statistical methods:	The results of this study were mostly descriptive rather than comparative with calculation of means, standard deviations, medians and 95% confidence intervals. Within-patient changes were studied and the rate of decline and rise in serum carbohydrate levels were calculated. Changes in overall means for safety parameters were calculated. Statistical testing was only performed on sodium, chloride and plasma osmolality. Symptom data were described and adverse events listed by ICD9.
SUMMARY – CONCLUSIONS:	
Efficacy results:	Pretreatment mean icodextrin and maltose levels were 0.3 mg/mL and 0.03 mg/mL, respectively. Steady-state mean levels after two years of icodextrin treatment were 4.8 mg/mL for icodextrin and 1.1 mg/mL for maltose. Levels of total icodextrin and maltose metabolite fell to pretreatment levels within 15 days of ceasing icodextrin treatment. Levels of icodextrin and maltose reached steady state on the 8th day after restarting treatment.
Safety results:	Mean CAPD symptoms increased slightly (from 4.4 ± 1.6 to 5.3 ± 2.4) on returning to glucose from icodextrin, but fell slightly (4.2 ± 2.7) after 3 weeks on glucose and again (3.1 ± 2.0) after returning to icodextrin. Eight patients reported sixteen adverse events. One patient withdrew on Day 35 of the study to receive a transplant. The only changes in safety laboratory parameters were slight rises in sodium and chloride during the glucose treatment period.
CONCLUSION:	Total icodextrin and metabolites were eliminated by simple first order kinetics with no evidence of a storage compartment.

Table 9.0 (Page 1 of 16)
Incidence of Adverse Events by COSTART Body System and Preferred Term
Related and Unrelated Events Were Considered For All Studies

		Control Group (N=347)		Icodextrin Group (N=493)		All Patients (N=840)	
COSTART Body System	COSTART Preferred Term	N	Percent	N	Percent	N	Percent
BODY GENERAL	PERITONITIS	88	25.4	130	26.4	218	26.0
	EXIT SITE INFECTION	58	16.7	73	14.8	131	15.6
	PAIN	43	12.4	48	9.7	91	10.8
	HEADACHE	23	6.6	43	8.7	66	7.9
	PAIN, ABDOMINAL	20	5.8	39	7.9	59	7.0
	FLU SYNDROME	21	6.1	35	7.1	56	6.7
	INJURY ACCIDENTAL	14	4.0	31	6.3	45	5.4
	ASTHENIA	27	7.8	28	5.7	55	6.5
	LAB TEST ABNORMAL	12	3.5	25	5.1	37	4.4
	PAIN CHEST	12	3.5	25	5.1	37	4.4
	PAIN BACK	18	5.2	22	4.5	40	4.8
	INFECTION	19	5.5	21	4.3	40	4.8
	FEVER	3	0.9	18	3.7	21	2.5
	PD CATHETER DYSFUNCTION	12	3.5	16	3.2	28	3.3
	MALAISE	7	2.0	10	2.0	17	2.0
	CYST	3	0.9	10	2.0	13	1.5
	EXIT SITE INFLAMATION	3	0.9	10	2.0	13	1.5
	HERNIA	12	3.5	8	1.6	20	2.4
	TUNNEL INFECTION	2	0.6	8	1.6	10	1.2
	ALLERGIC REACTION	13	3.7	7	1.4	20	2.4
	CELLULITIS	8	2.3	6	1.2	14	1.7
	INFECT VIRAL	2	0.6	6	1.2	8	1.0
	ABSCESS	6	1.7	5	1.0	11	1.3
	EFFLUENT BLOODY	4	1.2	5	1.0	9	1.1
	PAIN NECK	4	1.2	4	0.8	8	1.0

Only one event per patient per preferred term was counted.
Events are ordered within each Body System from highest to lowest incidence rates within the Icodextrin group.

Table 9 (Page 2 of 16)
Incidence of Adverse Events by COSTART Body System and Preferred Term
Related and Unrelated Events Were Considered For All Studies

COSTART Body System	COSTART Preferred Term	Control Group (N=347)		Icodextrin Group (N=493)		All Patients (N=840)	
		N	Percent	N	Percent	N	Percent
BODY GENERAL (CONT.)	CHILLS	2	0.6	4	0.8	6	0.7
	ABDOMEN ENLARGED	1	0.3	4	0.8	5	0.6
	CONTAMINATION	0	0.0	4	0.8	4	0.5
	EDEMA FACE	0	0.0	4	0.8	4	0.5
	MONILIA	0	0.0	4	0.8	4	0.5
	SEPSIS	3	0.9	3	0.6	6	0.7
	CLOUDY EFFLUENT	2	0.6	3	0.6	5	0.6
	PAIN FLANK	2	0.6	3	0.6	5	0.6
	INFECTION FUNGAL	1	0.3	3	0.6	4	0.5
	NEOPLASM	1	0.3	3	0.6	4	0.5
	MALNUTRITION	4	1.2	2	0.4	6	0.7
	PAIN CHEST SUBSTERNAL	3	0.9	2	0.4	5	0.6
	HD ACCESS DYSFUNCION	2	0.6	2	0.4	4	0.5
	INFECTION BACTIAL	1	0.3	2	0.4	3	0.4
	DEATH	0	0.0	2	0.4	2	0.2
	GANGRENE	0	0.0	2	0.4	2	0.2
	PAIN ON INFUSION	0	0.0	2	0.4	2	0.2
	ALTERED HORMONE LEVEL	1	0.3	1	0.2	2	0.2
	PAIN CHEST WALL	1	0.3	1	0.2	2	0.2
	CARCINOMA	0	0.0	1	0.2	1	0.1
	CHILLS FEVER	0	0.0	1	0.2	1	0.1
	EDEMA GENERAL	0	0.0	1	0.2	1	0.1
	EXIT SITE/TUNNEL INFECTION	0	0.0	1	0.2	1	0.1
	HEMMORRAGE RETROPERITONEAL	0	0.0	1	0.2	1	0.1
	HOSTILITY	0	0.0	1	0.2	1	0.1

Only one event per patient per preferred term was counted.
Events are ordered within each Body System from highest to lowest incidence rates within the Icodextrin group.

Table 9 (Page 3 of 16)
Incidence of Adverse Events by COSTART Body System and Preferred Term
Related and Unrelated Events Were Considered For All Studies

		Control Group (N=347)		Icodextrin Group (N=493)		All Patients (N=840)	
COSTART Body System	COSTART Preferred Term	N	Percent	N	Percent	N	Percent
BODY GENERAL (CONT.)	HYPERTROPHY	0	0.0	1	0.2	1	0.1
	INFECTION SUPERIMPOSED	0	0.0	1	0.2	1	0.1
	REACTION AGGRAVATION	0	0.0	1	0.2	1	0.1
	SHOCK	0	0.0	1	0.2	1	0.1
	SURGERY EXTREMITY	0	0.0	1	0.2	1	0.1
	MUCOUS MEMBRANE DISORDER	3	0.9	0	0.0	3	0.4
	ABDOMINAL SYNDROME ACUTE	1	0.3	0	0.0	1	0.1
	AMPUTATION	1	0.3	0	0.0	1	0.1
	HIV TEST POSITIVE	1	0.3	0	0.0	1	0.1
	IMMUNE SYSTEM DISORDER	1	0.3	0	0.0	1	0.1
	PAIN PELVIC	1	0.3	0	0.0	1	0.1
	PD CATHETER REPLACEMENT	1	0.3	0	0.0	1	0.1
CARDIOVASCULAR	HYPERTENSION	29	8.4	62	12.6	91	10.8
	HYPOTENSION	37	10.7	32	6.5	69	8.2
	VASCULAR DISORDER PERIPHERAL	13	3.7	17	3.4	30	3.6
	ANGINA PECTORIS	5	1.4	12	2.4	17	2.0
	INFARCT MYOCARDIAL	5	1.4	11	2.2	16	1.9
	HEART ARREST	3	0.9	11	2.2	14	1.7
	CARDIAC MURMUR	1	0.3	10	2.0	11	1.3
	CEREBROVASCULAR ACCIDENT	2	0.6	8	1.6	10	1.2
	PERICARDITIS	2	0.6	7	1.4	9	1.1
	CARDIOVASC DISORDER	0	0.0	7	1.4	7	0.8
	VASCULAR DISORDER	5	1.4	6	1.2	11	1.3
	TACHYCARDIA	6	1.7	4	0.8	10	1.2
	CORONARY ARTERY DISEASE	2	0.6	4	0.8	6	0.7

Only one event per patient per preferred term was counted.
Events are ordered within each Body System from highest to lowest incidence rates within the Icodextrin group.

Table 9 (Page 4 of 16)
Incidence of Adverse Events by COSTART Body System and Preferred Term
Related and Unrelated Events Were Considered For All Studies

COSTART Body System	COSTART Preferred Term	Control Group (N=347)		Icodextrin Group (N=493)		All Patients (N=840)	
		N	Percent	N	Percent	N	Percent
CARDIOVASCULAR (CONT.)	HEART FAILURE	2	0.6	4	0.8	6	0.7
	HEART FAIL RIGHT	2	0.6	4	0.8	6	0.7
	SYNCOPE	7	2.0	3	0.6	10	1.2
	HYPOTENSION POSTURAL	4	1.2	3	0.6	7	0.8
	ARRHYTHMIA	1	0.3	3	0.6	4	0.5
	CARDIOMEGALY	1	0.3	3	0.6	4	0.5
	ARTERIOSCLEROSIS	0	0.0	3	0.6	3	0.4
	PALPITATION	4	1.2	2	0.4	6	0.7
	HEMMORRAGE	1	0.3	2	0.4	3	0.4
	INFARCTION CEREBRAL	1	0.3	2	0.4	3	0.4
	THROMOBIS	1	0.3	2	0.4	3	0.4
	BRADYCARDIA	0	0.0	2	0.4	2	0.2
	CARDIOMYOPATHY	0	0.0	2	0.4	2	0.2
	EMBOLUS PULMONARY	0	0.0	2	0.4	2	0.2
	FIBRILLATION ATRIAL	0	0.0	2	0.4	2	0.2
	OCCLUSION CORONARY	0	0.0	2	0.4	2	0.2
	STENOSIS AORTIC	0	0.0	2	0.4	2	0.2
	THROMBOSIS CAROTID	0	0.0	2	0.4	2	0.2
	GANGRENE PERIPHAL	2	0.6	1	0.2	3	0.4
	MIGRAINE	2	0.6	1	0.2	3	0.4
	THROMBOPHLEBITIS DEEP	2	0.6	1	0.2	3	0.4
	FLUTTER ATRIAL	1	0.3	1	0.2	2	0.2
	EXTRASYSTOLES VENTRICULAR	0	0.0	1	0.2	1	0.1
	HEMMORRAGE CEREBRAL	0	0.0	1	0.2	1	0.1
	OCCLUSION	0	0.0	1	0.2	1	0.1

Only one event per patient per preferred term was counted.
Events are ordered within each Body System from highest to lowest incidence rates within the Icodextrin group.

Table 9 (Page 5 of 16)
Incidence of Adverse Events by COSTART Body System and Preferred Term
Related and Unrelated Events Were Considered For All Studies

		Control Group (N=347)		Icodextrin Group (N=493)		All Patients (N=840)	
COSTART Body System	COSTART Preferred Term	N	Percent	N	Percent	N	Percent
CARDIOVASCULAR (CONT.)	SURGERY HEART	0	0.0	1	0.2	1	0.1
	OCCLUSION CAROTID	2	0.6	0	0.0	2	0.2
	EMBOLUS	1	0.3	0	0.0	1	0.1
	PALLOR	1	0.3	0	0.0	1	0.1
	TACHYCARDIA SUPVENTRICULAR	1	0.3	0	0.0	1	0.1
	VASOSPASM	1	0.3	0	0.0	1	0.1
DIGESTIVE	DIARRHEA	33	9.5	40	8.1	73	8.7
	NAUSEA	17	4.9	35	7.1	52	6.2
	NAUSEA VOMITING	21	6.1	25	5.1	46	5.5
	DYSPEPSIA	13	3.7	25	5.1	38	4.5
	VOMITING	19	5.5	22	4.5	41	4.9
	CONSTIPATION	15	4.3	18	3.7	33	3.9
	ANOREXIA	11	3.2	17	3.4	28	3.3
	GASTRITIS	7	2.0	10	2.0	17	2.0
	GI DISORDER	4	1.2	9	1.8	13	1.5
	HEMMORRAGE GI	8	2.3	7	1.4	15	1.8
	STOOL ABNORMAL	4	1.2	6	1.2	10	1.2
	TOOTH DISORDER	2	0.6	6	1.2	8	1.0
	LIVER FUNCTION ABNORMAL	1	0.3	6	1.2	7	0.8
	GASTROENTERITIS	7	2.0	5	1.0	12	1.4
	RECTAL DISORDER	4	1.2	4	0.8	8	1.0
	FLATULANCE	3	0.9	4	0.8	7	0.8
	ABSCESS PERIODONTAL	2	0.6	4	0.8	6	0.7
	OBSTRUCTION INTESTINAL	2	0.6	4	0.8	6	0.7
	HEMMORAGE RECTAL	1	0.3	4	0.8	5	0.6

Only one event per patient per preferred term was counted.
Events are ordered within each Body System from highest to lowest incidence rates within the Icodextrin group.

Table 9 (Page 6 of 16)
Incidence of Adverse Events by COSTART Body System and Preferred Term
Related and Unrelated Events Were Considered For All Studies

COSTART Body System	COSTART Preferred Term	Control Group (N=347)		Icodextrin Group (N=493)		All Patients (N=840)	
		N	Percent	N	Percent	N	Percent
DIGESTIVE (CONT.)	HEMATEMESIS	0	0.0	4	0.8	4	0.5
	MONILIA ORAL	5	1.4	3	0.6	8	1.0
	CHOLELITHIASIS	4	1.2	3	0.6	7	0.8
	STOMACH ATONY	2	0.6	3	0.6	5	0.6
	DYSPHAGIA	1	0.3	3	0.6	4	0.5
	ULCER STOMACH	1	0.3	3	0.6	4	0.5
	COLITIS	2	0.6	2	0.4	4	0.5
	ESOPHAGITIS	2	0.6	2	0.4	4	0.5
	ILEUS	2	0.6	2	0.4	4	0.5
	PANCREATITIS	3	0.9	1	0.2	4	0.5
	CHOLECYSTITIS	1	0.3	1	0.2	2	0.2
	GI PERFORATION	1	0.3	1	0.2	2	0.2
	HEMMORRAGE GUM	1	0.3	1	0.2	2	0.2
	MELENA	1	0.3	1	0.2	2	0.2
	APPENDIX PERFORATED	0	0.0	1	0.2	1	0.1
	DIARRHEA BLOODY	0	0.0	1	0.2	1	0.1
	DISCOLOR TONGUE	0	0.0	1	0.2	1	0.1
	ERUCTATION	0	0.0	1	0.2	1	0.1
	HEPATITIS C	0	0.0	1	0.2	1	0.1
	JAUNDICE CHOLESTATIC	0	0.0	1	0.2	1	0.1
	LIVER DAMAGE	0	0.0	1	0.2	1	0.1
	MONILIA	0	0.0	1	0.2	1	0.1
	MONILIA GI	0	0.0	1	0.2	1	0.1
	NECROSIS INTESTINAL	0	0.0	1	0.2	1	0.1
	PROCTITIS	0	0.0	1	0.2	1	0.1

Only one event per patient per preferred term was counted.
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Table 9 (Page 7 of 16)
Incidence of Adverse Events by COSTART Body System and Preferred Term
Related and Unrelated Events Were Considered For All Studies

		Control Group (N=347)		Icodextrin Group (N=493)		All Patients (N=840)	
COSTART Body System	COSTART Preferred Term	N	Percent	N	Percent	N	Percent
DIGESTIVE (CONT.)	STOMATITIS	0	0.0	1	0.2	1	0.1
	ULCER DUODENUM	0	0.0	1	0.2	1	0.1
	ULCER DUODENUM HEMMORRAGE	0	0.0	1	0.2	1	0.1
	ULCER MOUTH	0	0.0	1	0.2	1	0.1
	ULCER PEPTIC	0	0.0	1	0.2	1	0.1
	NAUSEA VOMITING DIAR	2	0.6	0	0.0	2	0.2
	BEZOAR	1	0.3	0	0.0	1	0.1
	COLITIS PSEUDOMEMBRANOUS	1	0.3	0	0.0	1	0.1
	GINGIVITIS	1	0.3	0	0.0	1	0.1
	INTESTINE LARGE PERFORATION	1	0.3	0	0.0	1	0.1
	PANCREATITIS NECROSIS	1	0.3	0	0.0	1	0.1
	STENOSIS ESOPHAGEAL	1	0.3	0	0.0	1	0.1
	ULCER STOMACH HEMMORRAGE	1	0.3	0	0.0	1	0.1
ENDO	PARATHYROID DISORDER	6	1.7	5	1.0	11	1.3
	HYPOTHYROIDSM	4	1.2	3	0.6	7	0.8
	DIABETES MELLITUS	5	1.4	2	0.4	7	0.8
	ADRENAL DISORDER	1	0.3	1	0.2	2	0.2
	COMA DIABETIC	0	0.0	1	0.2	1	0.1
	THYROID DISORDER	0	0.0	1	0.2	1	0.1
HEMATOLOGIC AND LYMPHATIC	ANEMIA	39	11.2	55	11.2	94	11.2
	LEUKOCYTOSIS	4	1.2	15	3.0	19	2.3
	ANEMIA IRON DEFICIENCY	6	1.7	9	1.8	15	1.8
	ECCHYMOSIS	3	0.9	4	0.8	7	0.8
	LYMPHADENOPATHY	0	0.0	4	0.8	4	0.5
	FIBRIN INCREASE	0	0.0	3	0.6	3	0.4

Only one event per patient per preferred term was counted.
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Table 9 (Page 8 of 16)
Incidence of Adverse Events by COSTART Body System and Preferred Term
Related and Unrelated Events Were Considered For All Studies

COSTART Body System	COSTART Preferred Term	Control Group (N=347)		Icodextrin Group (N=493)		All Patients (N=840)	
		N	Percent	N	Percent	N	Percent
HEMATOLOGIC AND LYMPHATIC (CONT.)	THROMBOCYTOPENIA	2	0.6	2	0.4	4	0.5
	ALLOGRAFT REJECTION	1	0.3	2	0.4	3	0.4
	EOSINOPHILIA	4	1.2	1	0.2	5	0.6
	COAGULATION TIME INCREASE	1	0.3	1	0.2	2	0.2
	ALLOGRAFT THROMOSIS	0	0.0	1	0.2	1	0.1
	ANEMIA HYPOCHROMIC	0	0.0	1	0.2	1	0.1
	LEUKOPENIA	0	0.0	1	0.2	1	0.1
	LYMPHOMA LIKE REACTION	0	0.0	1	0.2	1	0.1
	LYMPHANGITIS	1	0.3	0	0.0	1	0.1
	MYELOMA	1	0.3	0	0.0	1	0.1
	POLYCYTHEMIA	1	0.3	0	0.0	1	0.1
	THROMBOCYTHEMIA	1	0.3	0	0.0	1	0.1
METABOLIC AND NUTRITION	HYPOKALEMIA	37	10.7	34	6.9	71	8.5
	HYPOPROTEINEMIA	32	9.2	34	6.9	66	7.9
	HYPERVOLEMIA	20	5.8	28	5.7	48	5.7
	EDEMA	17	4.9	28	5.7	45	5.4
	HYPERPHOSPHATEMIA	26	7.5	25	5.1	51	6.1
	HYPERGLYCEMIA	12	3.5	25	5.1	37	4.4
	DEHYDRATION	17	4.9	23	4.7	40	4.8
	EDEMA PERIPHERAL	29	8.4	18	3.7	47	5.6
	HYPERCALCEMIA	10	2.9	17	3.4	27	3.2
	PHOSPHATASE ALKALINE INCREASE	6	1.7	14	2.8	20	2.4
	WEIGHT INCREASE	9	2.6	12	2.4	21	2.5
	HYPONATREMIA	7	2.0	11	2.2	18	2.1
	WEIGHT DECREASE	4	1.2	11	2.2	15	1.8

Only one event per patient per preferred term was counted.
Events are ordered within each Body System from highest to lowest incidence rates within the Icodextrin group.

Table 9 (Page 9 of 16)
Incidence of Adverse Events by COSTART Body System and Preferred Term
Related and Unrelated Events Were Considered For All Studies

COSTART Body System	COSTART Preferred Term	Control Group (N=347)		Icodextrin Group (N=493)		All Patients (N=840)	
		N	Percent	N	Percent	N	Percent
METABOLIC AND NUTRITION (CONT.)	HYPERCHOLESTEREMIA	8	2.3	10	2.0	18	2.1
	HYPOCALCEMIA	6	1.7	10	2.0	16	1.9
	HYPOVOLEMIA	7	2.0	9	1.8	16	1.9
	SGPT INCREASE	3	0.9	9	1.8	12	1.4
	SGOT INCREASE	1	0.3	9	1.8	10	1.2
	HYPERKALEMIA	6	1.7	8	1.6	14	1.7
	HYPOCHLOREMIA	3	0.9	8	1.6	11	1.3
	HYPOMAGNESEMIA	4	1.2	7	1.4	11	1.3
	HYPOGLYCEMIA	9	2.6	6	1.2	15	1.8
	HYPOCHOLESTEREMIA	1	0.3	6	1.2	7	0.8
	ACIDOSIS	1	0.3	5	1.0	6	0.7
	GOUT	1	0.3	5	1.0	6	0.7
	HYPERLIPEMIA	4	1.2	4	0.8	8	1.0
	HYPOPHOSPHATEMIA	6	1.7	3	0.6	9	1.1
	ELECTROLYTE ABNORMALITY	4	1.2	3	0.6	7	0.8
	CREATININE INCREASE	2	0.6	3	0.6	5	0.6
	ULTRAFIL DECREASE	6	1.7	2	0.4	8	1.0
	CALCIUM DISORDER	3	0.9	2	0.4	5	0.6
	BUN INCREASE	0	0.0	2	0.4	2	0.2
	HEMOSIDEROSIS	0	0.0	2	0.4	2	0.2
	HYPOGLYCEMIC REACTION	0	0.0	2	0.4	2	0.2
	THIRST	0	0.0	2	0.4	2	0.2
	CREATINE PK INCREASE	1	0.3	1	0.2	2	0.2
	FERRITAN INCREASE	1	0.3	1	0.2	2	0.2
	OBESITY	1	0.3	1	0.2	2	0.2

Only one event per patient per preferred term was counted.
Events are ordered within each Body System from highest to lowest incidence rates within the Icodextrin group.

Table 9 (Page 10 of 16)
Incidence of Adverse Events by COSTART Body System and Preferred Term
Related and Unrelated Events Were Considered For All Studies

COSTART Body System	COSTART Preferred Term	Control Group (N=347)		Icodextrin Group (N=493)		All Patients (N=840)	
		N	Percent	N	Percent	N	Percent
METABOLIC AND NUTRITION (CONT.)	CYANOSIS	0	0.0	1	0.2	1	0.1
	HYPOXIA	0	0.0	1	0.2	1	0.1
	HYPOLIPEMIA	2	0.6	0	0.0	2	0.2
	CREATININE CLEARANCE DECREASE	1	0.3	0	0.0	1	0.1
	HEALING ABNORMALITY	1	0.3	0	0.0	1	0.1
	HYPERNATREMIA	1	0.3	0	0.0	1	0.1
MUSCULOSKELETAL	ARTHRALGIA	27	7.8	31	6.3	58	6.9
	ARTHRITIS	4	1.2	9	1.8	13	1.5
	MYALGIA	8	2.3	5	1.0	13	1.5
	CRAMPS LEG	5	1.4	5	1.0	10	1.2
	MYASTHENIA	1	0.3	5	1.0	6	0.7
	BONE FRACT SPONTANEOUS	6	1.7	4	0.8	10	1.2
	CRAMPING	4	1.2	4	0.8	8	1.0
	BONE DISORDER	1	0.3	4	0.8	5	0.6
	JOINT DISORDER	3	0.9	3	0.6	6	0.7
	PAIN BONE	1	0.3	2	0.4	3	0.4
	MYOPATHY	0	0.0	2	0.4	2	0.2
	BURSITIS	3	0.9	1	0.2	4	0.5
	OSTEOMYELITIS	1	0.3	1	0.2	2	0.2
	TENDON DISORDER	1	0.3	1	0.2	2	0.2
	PTOSIS	0	0.0	1	0.2	1	0.1
	ARTHRITIS RHEUMATOID	1	0.3	0	0.0	1	0.1
	ARTHROSIS	1	0.3	0	0.0	1	0.1
	NECROSIS BONE	1	0.3	0	0.0	1	0.1
NERVOUS	DIZZINESS	19	5.5	27	5.5	46	5.5

Only one event per patient per preferred term was counted.
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Table 9 (Page 11 of 16)
Incidence of Adverse Events by COSTART Body System and Preferred Term
Related and Unrelated Events Were Considered For All Studies

COSTART Body System	COSTART Preferred Term	Control Group (N=347)		Icodextrin Group (N=493)		All Patients (N=840)	
		N	Percent	N	Percent	N	Percent
NERVOUS (CONT.)	INSOMNIA	15	4.3	15	3.0	30	3.6
	DEPRESSION	13	3.7	13	2.6	26	3.1
	CONFUSION	5	1.4	9	1.8	14	1.7
	NEUROPATHY	5	1.4	9	1.8	14	1.7
	NEURITIS PERIPHERAL	11	3.2	8	1.6	19	2.3
	HYPESTHESIA	4	1.2	6	1.2	10	1.2
	GAIT ABNORMAL	1	0.3	6	1.2	7	0.8
	SOMNOLENCE	13	3.7	5	1.0	18	2.1
	PARESTHESIA	3	0.9	5	1.0	8	1.0
	ANXIETY	3	0.9	4	0.8	7	0.8
	CONVULSION	2	0.6	4	0.8	6	0.7
	THINKING ABNORMAL	1	0.3	4	0.8	5	0.6
	DRY MOUTH	5	1.4	3	0.6	8	1.0
	HYPERTONIA	2	0.6	3	0.6	5	0.6
	TREMOR	1	0.3	3	0.6	4	0.5
	HYPERKINESIA	2	0.6	2	0.4	4	0.5
	CEREBROVASCULAR ACCIDENT	1	0.3	2	0.4	3	0.4
	NEURALGIA	1	0.3	2	0.4	3	0.4
	NEUROSIS	1	0.3	2	0.4	3	0.4
	PARALYSIS FACIAL	1	0.3	2	0.4	3	0.4
	AMNESIA	1	0.3	1	0.2	2	0.2
	ATAXIA	1	0.3	1	0.2	2	0.2
	NERVOUSNESS	1	0.3	1	0.2	2	0.2
	AGITATION	0	0.0	1	0.2	1	0.1
	APHASIA	0	0.0	1	0.2	1	0.1

Only one event per patient per preferred term was counted.
Events are ordered within each Body System from highest to lowest incidence rates within the Icodextrin group.

Table 9 (Page 12 of 16)
Incidence of Adverse Events by COSTART Body System and Preferred Term
Related and Unrelated Events Were Considered For All Studies

COSTART Body System	COSTART Preferred Term	Control Group (N=347)		Icodextrin Group (N=493)		All Patients (N=840)	
		N	Percent	N	Percent	N	Percent
NERVOUS (CONT.)	CONVULSION GRAND MAL	0	0.0	1	0.2	1	0.1
	DELUSIONS	0	0.0	1	0.2	1	0.1
	EMOTIONAL LABILITY	0	0.0	1	0.2	1	0.1
	HEMIPLEGIA	0	0.0	1	0.2	1	0.1
	HYPOKINESIA	0	0.0	1	0.2	1	0.1
	TWITCH	0	0.0	1	0.2	1	0.1
	MOVEMENT DISORDER	2	0.6	0	0.0	2	0.2
	VASODILATION	2	0.6	0	0.0	2	0.2
	DREAM ABNORMAL	1	0.3	0	0.0	1	0.1
	PERSONALITY DISORDER	1	0.3	0	0.0	1	0.1
	REFLEXES DECREASED	1	0.3	0	0.0	1	0.1
	URINARY RETENTION	1	0.3	0	0.0	1	0.1
	VERTIGO	1	0.3	0	0.0	1	0.1
RESPIRATORY	UPPER RES INFECTION	46	13.3	74	15.0	120	14.3
	COUGH INCREASE	13	3.7	35	7.1	48	5.7
	DYSPNEA	24	6.9	26	5.3	50	6.0
	RHINITIS	14	4.0	20	4.1	34	4.0
	PHARYNGITIS	5	1.4	15	3.0	20	2.4
	PNEUMONIA	8	2.3	12	2.4	20	2.4
	SINUSITIS	7	2.0	11	2.2	18	2.1
	EDEMA LUNG	2	0.6	6	1.2	8	1.0
	EFFUS PLEURAL	2	0.6	6	1.2	8	1.0
	BRONCHITIS	6	1.7	5	1.0	11	1.3
	HICCUP	1	0.3	5	1.0	6	0.7
	LUNG DISORDER	6	1.7	4	0.8	10	1.2

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Table 9 (Page 13 of 16)
Incidence of Adverse Events by COSTART Body System and Preferred Term
Related and Unrelated Events Were Considered For All Studies

COSTART Body System	COSTART Preferred Term	Control Group (N=347)		Icodextrin Group (N=493)		All Patients (N=840)	
		N	Percent	N	Percent	N	Percent
RESPIRATORY (CONT.)	EPISTAXIS	5	1.4	4	0.8	9	1.1
	SPUTUM INCREASE	1	0.3	3	0.6	4	0.5
	RESPIRATORY DISORDER	5	1.4	2	0.4	7	0.8
	ATELECTASIS	2	0.6	2	0.4	4	0.5
	PLEURAL DISORDER	2	0.6	1	0.2	3	0.4
	LARYNGITIS	1	0.3	1	0.2	2	0.2
	PNEUMONIA ASPIRATION	1	0.3	1	0.2	2	0.2
	APNEA	0	0.0	1	0.2	1	0.1
	ASTHMA	0	0.0	1	0.2	1	0.1
	HYPERTENSION PULMONARY	0	0.0	1	0.2	1	0.1
	VOICE ALTERATION	0	0.0	1	0.2	1	0.1
SKIN	RASH	16	4.6	50	10.1	66	7.9
	PRURITUS	23	6.6	27	5.5	50	6.0
	ULCER SKIN	13	3.7	16	3.2	29	3.5
	SKIN DISORDER	18	5.2	11	2.2	29	3.5
	SKIN DRY	3	0.9	10	2.0	13	1.5
	DERMATITIS EXFOLIATIVE	1	0.3	9	1.8	10	1.2
	RASH VESICULAR BULLOUS	9	2.6	6	1.2	15	1.8
	ECZEMA	1	0.3	6	1.2	7	0.8
	FURUNCULOSIS	4	1.2	5	1.0	9	1.1
	NAIL DISORDER	2	0.6	5	1.0	7	0.8
	CARCINOMA SKIN	0	0.0	4	0.8	4	0.5
	PSORIASIS	2	0.6	3	0.6	5	0.6
	ERYTHEMA NODOSUM	0	0.0	3	0.6	3	0.4
	SKIN DISCOLOR	0	0.0	3	0.6	3	0.4

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Table 9 (Page 14 of 16)
Incidence of Adverse Events by COSTART Body System and Preferred Term
Related and Unrelated Events Were Considered For All Studies

		Control Group (N=347)		Icodextrin Group (N=493)		All Patients (N=840)	
COSTART Body System	COSTART Preferred Term	N	Percent	N	Percent	N	Percent
SKIN (CONT.)	HERPES ZOSTER	9	2.6	2	0.4	11	1.3
	URTICARIA	0	0.0	2	0.4	2	0.2
	HERPES SIMPLEX	3	0.9	1	0.2	4	0.5
	RASH MACULOPAPULAR	3	0.9	1	0.2	4	0.5
	ACNE	2	0.6	1	0.2	3	0.4
	ALOPECIA	0	0.0	1	0.2	1	0.1
	DERM FUNG	0	0.0	1	0.2	1	0.1
	ERYTHEMA MULTIFORME	0	0.0	1	0.2	1	0.1
	HYPERTROPHY SKIN	0	0.0	1	0.2	1	0.1
	NODULE SUBCUTANEOUS	0	0.0	1	0.2	1	0.1
	SWEAT	0	0.0	1	0.2	1	0.1
	DIAPHORESIS	1	0.3	0	0.0	1	0.1
	NECROSIS SKIN	1	0.3	0	0.0	1	0.1
	PRURITIS	1	0.3	0	0.0	1	0.1
SPECIAL SENSES	EYE DISORDER	6	1.7	13	2.6	19	2.3
	EAR DISORDER	3	0.9	10	2.0	13	1.5
	VISION ABNORMALITY	4	1.2	8	1.6	12	1.4
	CATARACT NOS	3	0.9	7	1.4	10	1.2
	CONJUNCTIVITIS	8	2.3	6	1.2	14	1.7
	AMBLYOPIA	0	0.0	5	1.0	5	0.6
	HEMMORRAGE EYE	4	1.2	4	0.8	8	1.0
	PAIN EAR	2	0.6	4	0.8	6	0.7
	RETINAL DISORDER	2	0.6	4	0.8	6	0.7
	RETINAL VASCULAR DISORDER	0	0.0	3	0.6	3	0.4
	PAIN EYE	2	0.6	2	0.4	4	0.5

Only one event per patient per preferred term was counted.
Events are ordered within each Body System from highest to lowest incidence rates within the Icodextrin group.

Table 9 (Page 15 of 16)
Incidence of Adverse Events by COSTART Body System and Preferred Term
Related and Unrelated Events Were Considered For All Studies

COSTART Body System	COSTART Preferred Term	Control Group (N=347)		Icodextrin Group (N=493)		All Patients (N=840)	
		N	Percent	N	Percent	N	Percent
SPECIAL SENSES (CONT.)	DRY EYE	1	0.3	2	0.4	3	0.4
	CATARACT	0	0.0	2	0.4	2	0.2
	VITREOUS DISORDER	2	0.6	1	0.2	3	0.4
	TINNITUS	1	0.3	1	0.2	2	0.2
	TASTE LOSS	0	0.0	1	0.2	1	0.1
	VESTIBULAR DISORDER	0	0.0	1	0.2	1	0.1
	CORNEAL OPACITY	2	0.6	0	0.0	2	0.2
	HEMMORAGE RETINAL	2	0.6	0	0.0	2	0.2
	BLIND	1	0.3	0	0.0	1	0.1
	DEAF	1	0.3	0	0.0	1	0.1
	GLAUCOMA	1	0.3	0	0.0	1	0.1
	LACRIMATION DISORDER	1	0.3	0	0.0	1	0.1
	OTITIS MEDIA	1	0.3	0	0.0	1	0.1
	TASTE PERVERS	1	0.3	0	0.0	1	0.1
	ULCER CORNEAL	1	0.3	0	0.0	1	0.1
UROGENITAL	INFECTION URINARY TRACT	16	4.6	13	2.6	29	3.5
	HEMATURIA	7	2.0	7	1.4	14	1.7
	DYSURIA	2	0.6	5	1.0	7	0.8
	PAIN KIDNEY	2	0.6	5	1.0	7	0.8
	NEOPLASM BREAST	1	0.3	4	0.8	5	0.6
	IMPOTENCE	0	0.0	4	0.8	4	0.5
	CYSTITIS	4	1.2	3	0.6	7	0.8
	MONILIA VAGINA	2	0.6	3	0.6	5	0.6
	VAGINITIS	1	0.3	3	0.6	4	0.5
	LEUKORRHEA	0	0.0	3	0.6	3	0.4

Only one event per patient per preferred term was counted.
Events are ordered within each Body System from highest to lowest incidence rates within the Icodextrin group.

Table 9(Page 16 of 16)
Incidence of Adverse Events by COSTART Body System and Preferred Term
Related and Unrelated Events Were Considered For All Studies

COSTART Body System	COSTART Preferred Term	Control Group (N=347)		Icodextrin Group (N=493)		All Patients (N=840)	
		N	Percent	N	Percent	N	Percent
UROGENITAL (CONT.)	PROSTATIC DISORDER	0	0.0	3	0.6	3	0.4
	KIDNEY POLYCYSTIC	1	0.3	2	0.4	3	0.4
	ANURIA	0	0.0	2	0.4	2	0.2
	BREAST FIBROCYST	0	0.0	2	0.4	2	0.2
	MENSTRUAL DISORDER	0	0.0	2	0.4	2	0.2
	MENORRHAGIA	3	0.9	1	0.2	4	0.5
	EDEMA SCROTUM	2	0.6	1	0.2	3	0.4
	UREMIA	2	0.6	1	0.2	3	0.4
	EDEMA GENITAL	1	0.3	1	0.2	2	0.2
	URINARY FREQUENCY	1	0.3	1	0.2	2	0.2
	URINARY URGENCY	1	0.3	1	0.2	2	0.2
	EDEMA LABIA	0	0.0	1	0.2	1	0.1
	GYNECOMASTIA	0	0.0	1	0.2	1	0.1
	HEMMORRAGE UTERINE	0	0.0	1	0.2	1	0.1
	KIDNEY CALCULUS	0	0.0	1	0.2	1	0.1
	LACTATION FEMALE	0	0.0	1	0.2	1	0.1
	MENOPAUSE	0	0.0	1	0.2	1	0.1
	NECROSIS KIDNEY TUBULULAR	0	0.0	1	0.2	1	0.1
	NEPHRECTOMY	0	0.0	1	0.2	1	0.1
	URINARY ABNORMALITY	0	0.0	1	0.2	1	0.1
	URINARY TRACT DISORDER	2	0.6	0	0.0	2	0.2
	CARCINOMA PROSTATE	1	0.3	0	0.0	1	0.1
	KIDNEY FUNCTION ABNORMAL	1	0.3	0	0.0	1	0.1
	VULVOVAGINAL DISORDER	1	0.3	0	0.0	1	0.1

Only one event per patient per preferred term was counted.
Events are ordered within each Body System from highest to lowest incidence rates within the Icodextrin group.